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REC'D

CIRCULATES

- 1 *Recurrent Urinary Infections in Adult Women—The Role of Intestinal Enterobacteria*
THOMAS A. STAMEY, M.D., MARY TIMOTHY, MARCIA MILLAR, and GLADYS MIHARA
- 20 *Therapeutic Abortions—A Review of 567 Cases*
PAUL H. BRENNER, M.D., EDWARD J. KIRSHEN, M.D., and JOSEPH M. DIDIO, M.D.
- 28 *Therapeutic Abortions in California* E. W. JACKSON, M.D., M. TASHIRO, M.S., and G. C. CUNNINGHAM, M.D.
- 34 *Multiphasic Health Testing in the Clinic Setting* JOSEPH LA DOU, M.D.
- 38 *Cancer of the Pancreas in California, 1942-1967—The California Tumor Registry Experience*
LAWRENCE STIRLING KRAIN, M.D., M.P.H.

MEDICAL PROGRESS

- 42 *Phenylketonuria and Its Variations—A Review of Recent Developments*
MILAN E. BLASKOVICS, M.D., and THOMAS L. NELSON, M.D.

MEDICAL STAFF CONFERENCE

- 58 *Current Concepts in the Treatment of Hypertension* Discussion by KENNETH L. MELMON, M.D.

68 IMPORTANT ADVANCES IN CLINICAL MEDICINE—Pediatrics

- 75 EDITORIALS—*On Cutting Costs in Health Care • Phenylketonuria, the Inborn Errors of Metabolism, and Clinical Research—1971 • Dealing in Futures—Part I: In Medicine and Health Care*

★ 81 THE QUESTION:

Shall Organized Medicine be Unified, or Separate?

CASE REPORT

- 84 *Giant Cell Arteritis with Myositis and Myocarditis*
L. JAMES KENNEDY, JR., M.D., and M. J. MITCHINSON, M.D., M.R.C.PATH.

FRONTIERS OF PSYCHIATRY AND MEDICINE

- 88 *New Methods of Psychiatric Treatment* DON E. FLINN, M.D.

96 LETTERS TO THE EDITOR

IN THE FOREFRONT

- 100 *The Certified Hospital Admission Program*
JAMES J. SCHUBERT, M.D., JAMES BRAMHAM, M.D., FRANK SCHIRO, M.D., and H. JOHN RUSH, M.D.

MEDICINE IN PERSPECTIVE

- 102 *The Practice of Medicine in the Bush Country of Ghana* MARLENE E. LONG, M.D.

PUBLIC HEALTH REPORT

- 106 *Air Pollution, Health Effects and Urban Growth* LOUIS F. SAYLOR, M.D.

INFORMATION

- 108 *Congenital Heart Disease in the First Year of Life*
SIDNEY BLUMENTHAL, M.D., and MARY JANE JESSE, M.D.

★ CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII (See Advertising Page 7)

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Call it what you will, it may be premalignant.

Before

3/29/67 Before therapy with 5%-FU cream. Patient P. T. shows a moderately severe solar keratotic involvement. Note residual scarring from the previous cryosurgical and electrosurgical procedures on forehead and ridge of nose adjacent to periauricular area.

After

6/12/67 Seven weeks after cessation of therapy. Reactions have subsided. Residual scarring is not seen except for that due to prior surgery. Inflammation has disappeared and face is clear of keratotic lesions.





Recurrent Urinary Infections in Adult Women

The Role of Introital Enterobacteria

THOMAS A. STAMEY, M.D., MARY TIMOTHY, MARCIA MILLAR AND
GLADYS MIHARA, *Stanford*

INTESTINAL BACTERIA are recognized as the reservoir for *E. coli* urinary infections;¹⁻⁴ within this reservoir, however, the presence and distribution of fecal *E. coli* is essentially the same as in persons who never have urinary infections.⁴ Thus, identification of intestinal bacteria as the ultimate source of urinary infections has not explained the difference between women who are susceptible to infections and those who seem resistant.

Because bacterial persistence in the male with recurrent urinary infections is related to the prostate and urethra rather than the kidney,⁵ it seemed appropriate to examine the vaginal vestibule and the urethra of adult women with recurrent urinary infections. Our interest was further stimulated by the observation that the bacterial flora of the vaginal vestibule and urethral mucosa (hereafter referred to jointly as the introitus) of women who never have urinary infections is substantially different from those with recurrent infections. Specifically, the introitus of premenopausal women resistant to urinary infections rarely shows enterobacteria;⁶ when occasionally cultured, the numbers of *E. coli* are either exceedingly small or only transiently present. We noted in 1967 that women with recurrent infections, in contrast to normal subjects, have substantial numbers of pathogenic

bacteria that persist on these mucosal surfaces.⁷ We report here our observations that the establishment, persistence, and occurrence of these bacteria in large numbers on the vaginal vestibule and urethra immediately before infection determines the recurrence of bacteriuria in adult women.

Methods

Selection of Cases:

Adult women with bacteriologically documented recurrent bacteriuria, with or without a history of chills, fever and flank pain, were selected for investigation. Requirements for admission to the study were to maintain frequent outpatient visits while asymptomatic (about every two weeks), to consult us immediately at the first sign of symptoms, to stop all forms of vaginal douching or medication, and to take no antimicrobial agents without our expressed permission. Close contact and excellent cooperation were assured by not only frequent office visits but also interim telephone calls, and by limiting the professional involvement with the patients to three people: a physician, a research worker, and a nurse.

Collection of Specimens:

1. Vaginal vestibule: Each woman was placed on the cystoscopy table in a semi-sitting position with her legs in stirrups. The nurse, wearing sterile rubber gloves, spread the labia and swabbed

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the vaginal vestibule with two sterile cotton applicator sticks held together; this maneuver was performed in a circular motion covering all four quadrants at the level of the hymenal ring. The applicator sticks were placed in a test tube containing 5 ml of transport broth (Earle's balanced salt solution, Microbiological Associates, Bethesda, Md.) or sterile saline solution and immediately refrigerated.

A sterile wooden spatula or cotton tipped applicator stick was gently scraped along the wall of the deep vestibule or mid-vaginal area, the material obtained spread on a glass slide, and the slide placed in 95 percent alcohol.

A strip of nitrazine indicator paper was left in contact with the vaginal vestibule until moist enough to give a color indication of the pH.

2. Urethral and midstream urine cultures: After the vaginal specimen was obtained, the patient initiated voiding from the same position on the cystoscopy table. The nurse maintained separation of the labia with one hand and collected the first voided 5 to 10 ml by holding a culture tube 1 cm from the urethral meatus; this culture, representative of the urethral flora, was labeled VB_1 , the symbol for voided bladder 1. As the woman continued to void, a midstream aliquot (labeled VB_2) was collected in a similar fashion. All specimens were refrigerated within three minutes and cultured within one to three hours.

About 10 percent of our patients are unable to void on the cystoscopy table with a nurse in attendance. These women were carefully instructed in the collection technique and permitted to obtain their own specimens by sitting on the back edge of the toilet seat, holding the labia apart with one hand, and collecting the specimens as described above.

3. Male consorts of patients were studied by culturing first voided morning specimens divided into urethral and midstream aliquots. When positive for Gram-negative bacteria, they were examined in the outpatient unit where complete specimens, including prostatic fluid, were obtained by methods previously described.⁵

Definition of Bladder Bacteriuria:

Bacteriuria was defined as the presence of 10^5 or more bacteria per ml of a single species in the midstream urine specimen (VB_2) when obtained by the nurse from the patient on the cystoscopy

table in the manner described.⁸ It must be recognized that, even with this rigorously exacting technique of collecting a clean midstream urine, some enterobacteria will contaminate otherwise sterile midstream urine in the presence of heavy enterobacterial colonization of the introitus. Rarely, however, did the degree of contamination of the midstream urine exceed 1000 enterobacteria per ml.

Further evidence (obtained at the suggestion of Dr. A. Braude) that these low bacterial counts in the midstream urine did not represent suppressed bacteriuria was obtained by incubating an aliquot of midstream urine. Without exception, the smallest colony counts, even 1 to 10 Gram-negative bacteria per ml, grew to $>10^5$ bacteria per ml during overnight incubation.

The colony count in the urethral aliquot (VB_1) was similar to that of the midstream specimens, as would be expected, in the presence of bladder infection.

Bacteriologic Methods:

The culture fluid from the vaginal vestibule was vigorously agitated on a laboratory mixer and the cotton applicator sticks discarded. Culturing of the 5 ml of transport broth (vaginal vestibule), VB_1 and VB_2 urines was performed as follows:

1. Aerobic cultures: 0.1 ml of the vaginal vestibule, VB_1 and VB_2 specimens were cultured on whole plates of 5 percent sheep blood and eosin-methylene-blue (EMB) agars. A 10^{-2} and 10^{-4} dilution of the vaginal vestibule and a 10^{-2} dilution of the VB_1 aliquot was similarly streaked on blood and EMB agars. All cultures were incubated in 5 percent CO_2 at $37^\circ C$ for 24 hours, and were rechecked at 48 hours after standing at room temperature for 24 hours. If no growth was present at 24 hours, they were reincubated for an additional day.

2. Anaerobic cultures: A set of plates, identical to those for aerobic culture, was made for anaerobic incubation in sealed GasPak® (Baltimore Biological Laboratories) jars placed at $37^\circ C$ for four days. Plates were read immediately after removal from the GasPak jars. On all patients anaerobic cultures were performed at least once a month, and at any time symptoms developed.

3. Mycoplasma cultures: 0.2 ml of the vaginal vestibule, VB_1 and VB_2 specimens were inoculated

into Shepard's U-9 broth,⁹ incubated at 37°C in 5 percent CO₂, and held for two weeks before counting as negative.

From each of the three specimens 0.01 ml was inoculated as a single drop on a confined area of Shepard's A-5c agar¹⁰ and incubated in 5 percent CO₂ for 72 hours. The agar area was removed as a block, stained with methylene blue and a 22 mm cover slip applied; mycoplasma units were counted under 100X magnification, and reported as T-strain units per ml. Mycoplasma cultures were performed at least three times on every patient.

4. Slides: Three ml of the vaginal vestibule and VB₁ aliquots were spun at 2,000 rpm for 20 minutes. Wet mounts of the sediment were made and observed for epithelial cells, leukocytes, yeasts, trichomonas, and bacteria. All wet mounts were saved and Gram-stained. Papanicolaou stains were made of the vaginal smear. In addition, 1.0 ml of the VB₁ urine sample was mixed with 1.0 ml of 95 percent ethyl alcohol and passed through a 0.45 micron membrane filter. The filter was attached to a glass slide, placed in 95 percent alcohol, and also stained by the standard Papanicolaou method.

5. Banking of Gram-negative bacteria: As was shown in previous studies,⁶ and as will be seen in this paper, the VB₁ culture usually reflects the vaginal vestibule flora, but the number of organisms is less in the VB₁ specimen in patients without bladder bacteriuria. In several patients without bladder infections, but with *E. coli* on the vaginal vestibule and in the VB₁ culture, five individual colonies were picked and serotyped from each site; usually all ten, and at least nine out of ten colonies proved to be of the same serotype for any individual patient. Thus, when the specimens were collected by the nurse from the patient on the cystoscopy table, five to ten colonies of similar appearing Gram-negative bacteria were picked from the VB₁ specimen as representative of the introital flora. They were banked by touching five to ten representative colonies taken in random fashion and streaked in duplicate on 1.5 percent nutrient agar slants. The slants were incubated for 24 hours at 37°C, sealed with a cork dipped in melted paraffin and stored in a box free from direct light. When the VB₁ and VB₂ specimens were self-caught by the patient, the introital colonies, in the absence of bacteriuria, were chosen from the VB₂ specimen. When Gram-negative bac-

teria were occasionally found on the vaginal vestibule but were not present in either the VB₁ or VB₂, the vaginal bacteria were banked. In the presence of bladder bacteriuria, organisms were banked in duplicate from both the VB₂ and the vaginal vestibule. When Gram-negative bacteria of the same species seemed to vary in colonial morphology, sensitivity or biochemical pattern, they were banked as separate organisms. Thus, representative colonies of all Gram-negative bacteria were banked at each visit.

6. Serologic classification: Rabbit antisera, prepared by immunization with standard O antigens of *E. coli*, were obtained from the Communicable Disease Center, U.S. Public Health Center, Atlanta, Georgia. Sera for 148 O groups were available. The technique for O grouping was that reported by Edwards and Ewing¹¹ and was identical to the procedure used by Vosti and his colleagues.³ Strains which could not be grouped due to self-agglutination were classified as "self-agglutinating" (SA), while those strains which failed to be agglutinated by any antisera were classified as "non-typable" (NT). Among the non-typable strains, no distinction was given to those strains which had a "rough" colonial morphologic appearance.

Antigenic identity for strains of *Proteus mirabilis* was determined by the swarming techniques of Dienes,¹² and confirmed by serogrouping through the courtesy of Dr. Norman Hinton, Professor and Chairman of the Department of Bacteriology, University of Toronto. All strains of *P. mirabilis* isolated repeatedly from the same patient were shown by Dr. Hinton to be of the same O serogroup; all such isolates from the same patient also showed identity by Dienes swarming.

7. Antimicrobial sensitivity testing: The minimal inhibitory concentration (MIC) of several antimicrobial agents was determined against each organism causing bacteriuria as well as the next strains to appear on the introitus after initiation of therapy. The MIC was determined by the Ericsson method of quantitating disc diffusion,¹³ but Mueller-Hinton agar with 30 minutes prediffusion (which had been substituted in establishing the regression curves) was used in the determination of each MIC. Sulfonamide sensitivities were performed according to the method of Bauer and Sherris;¹⁴ results are reported as resistant (R) or sensitive (S), but we have also indicated the actual zone sizes.

TABLE 1.—General Data on Ten Women

Patient	Age	Menses	Supplemental Hormone	Years Since First Infection	Past History of Chills, Fever, and Flank Pain	Intravenous Urogram	Documented Bacteriuric Episodes* Antedating Study		D. Place Site
							Date	Organism	
A	27	Normal	----	3	Yes (rare)	Normal	3/ 7/68 2/20/69 11/11/69	Proteus Klebsiella E. coli	(4/5)
B	32	Normal	Sequential oral contraceptive	15	No	Congenital left ureteral stump	2/18/70	E. coli 075	(2/)
C	26	Normal	----	3	Yes (severe)	Right middle calyx irregular with loss of pyramid	12/10/68 8/27/70	E. coli E. coli	(9/)
D	68	Post Menopausal	Conjugated estrogen	6	No	Normal	12/ 1/65 1/ 4/66 3/31/70	E. coli 075 E. coli 075 E. coli 075	(4/)
E	26	Normal	----	4	Yes (1st Infection)	Normal	1/ 3/70 4/23/70	E. coli E. coli 018	(4/)
F	30	Normal	Combination oral contraceptive	9	Yes	Normal	12/15/69	E. coli	(3/)
G	55	Post Menopausal	Conjugated estrogen	28	No	Normal	4/26/66 6/10/69 9/ 2/69	E. coli E. coli E. coli	(1/)
H	52	Partial Hysterect	Conjugated estrogen	32	Yes	Normal	7/ 5/66	Proteus	(8/)
J	19	Normal Pregnant	----	1	Yes	----	1/23/70	E. coli	(1/)
K	49	Normal	----	14	Yes	Normal	5/24/68 11/13/69	E. coli E. coli 073	(12/)

Legend: E. coli (08), etc.=0-antigen serogroup of E. coli. P. mirabilis (048), etc.=0-antigen serogroup.

*Documented bacteriuric episodes refers to only those proven by culture at Stanford.

In comparing serial determinations of the MIC of antimicrobial agents for the same strain of bacteria, Ericsson has pointed out that the variation in MIC determinations using the quantitative disc is -50 to +100 percent (\pm one dilution in two-fold steps), and that this is about the same error that occurs in tube dilution studies.¹⁵

Results

Bacteriuric Episodes:

Eight of the first ten patients admitted to the study have been followed through 17 episodes of bacteriuria (Table 1); one patient had five infec-

tions, one had three, three had two, three had one each, and two had none. Thirteen of the 17 infections were caused by E. coli, four by P. mirabilis (three in the same patient, Patient A). Their past history included 19 additional documented instances of bacteriuria proven by culture at Stanford (Table 1); sixteen of these previous infections were caused by E. coli, two by P. mirabilis, and one by Klebsiella.

General Characteristics:

Except for one patient (Patient J) whose only previous infection was within one year of admission to the study, all other first infections oc-

2/1

24

13

Relation of Bacteriuria to The Introital Flora:

The bacteriologic course of four representative patients from Table 1 are presented in Charts 1 (Patient C), 2 (Patient B), 3 (Patient H), and 4 (Patient D). The first bladder infections presented in Chart 1 (*E. coli* NT), Chart 2 (*E. coli* 075), and Chart 4 (*E. coli* 075) are not counted among the 17 bacteriuric episodes analyzed in this report; these three patients were placed on the study at the time of this infection and hence previous introital cultures are not available. As seen in these four charts, each bladder infection was determined by the presence of the infecting

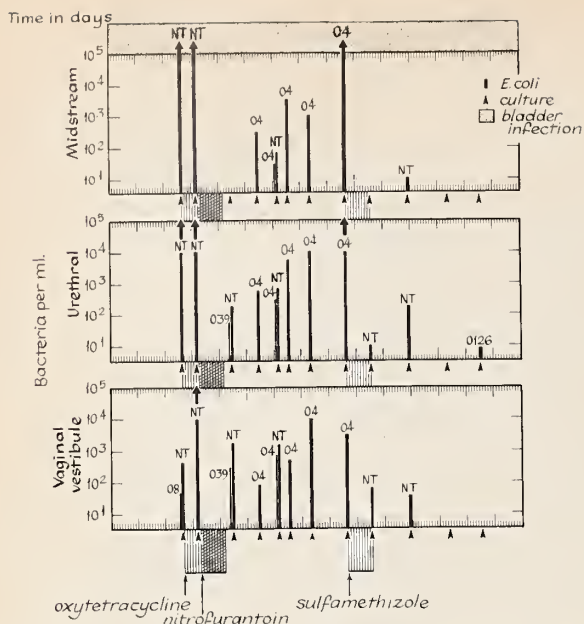


Chart 1.—Enterobacterial relationship of the vaginal vestibule, urethral, and midstream cultures in a 26-year-old, white, married woman (Patient C in Table 1). The only Gram-negative enterobacteria cultured were *E. coli*; the culture symbol (\blacktriangle), without overlying vertical bars, indicates the complete absence of Gram-negative enterobacteria. The serogroup of *E. coli* appears at the top of each solid bar; NT is a nontypable *E. coli*.

The patient had a three-year history of recurrent chills, fever, and flank pain. These data show that the *E. coli* 04 bacteriuric episode was preceded by the establishment of large numbers of introital *E. coli* 04 before the occurrence of the bacteriuria. Since the last culture (12/16/70) shown in this chart, ten additional cultures have been obtained at intervals of two weeks. The patient's introital bacteriology, except for *S. faecalis*, reverted to normal and her urinary infections ceased for five months. In the past month, however, *E. coli* 04 again appeared on the introitus and 30 days later was in the bladder.

strain on the vaginal vestibule. These figures should be interpreted with the realization that bacterial colonization of the introitus often contaminates an otherwise sterile midstream specimen unless the nurse collects it very late in the midstream. Moreover, contamination is all the more likely since the introitus is not cleaned or washed in these studies before the specimens are collected.

With two exceptions, all 17 episodes of bacteriuria were preceded by the establishment of the infecting strain on the introitus (Table 1). The first exception is the *E. coli* 016 bacteriuria in Patient B (Table 1); a 91-day lapse between outpatient visits after the last culture shown in Chart 2 prevented culturing of the introital flora

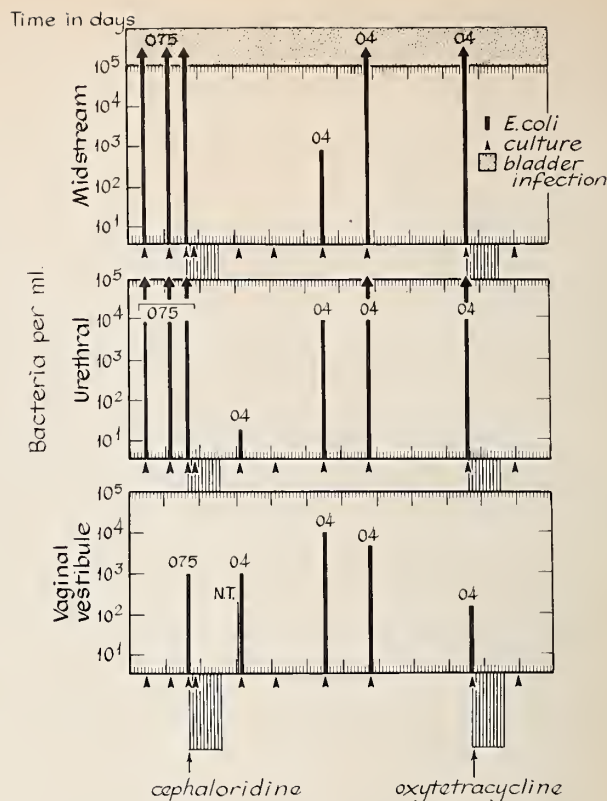


Chart 2.—Enterobacterial relationship of the vaginal vestibule, urethral, and midstream cultures in a 32-year-old, white, married woman (Patient B in Table 1). The only Gram-negative enterobacteria cultured were *E. coli*; the culture symbol (\blacktriangle), without overlying vertical bars, indicates the complete absence of Gram-negative enterobacteria. The serogroup of *E. coli* appears at the top of each solid bar; NT is nontypable *E. coli*.

Except for one stay in hospital with her first pregnancy at the age of 17, the patient was free of urinary infections until age 31 when a series of recurrences resulted in referral to Stanford. She was found to have a congenital left ureteral stump and a urethral diverticulum. Despite these two anatomical abnormalities, her recurrences were reinfections. The *E. coli* 04 responsible for her second bacteriuric episode appeared on the introitus first, similar to other infections in women without congenital abnormalities. Following the single post-treatment culture for her 04 bladder infection (shown in the chart) she was seen 91 days later (Table 1), without interval introital cultures, and had an *E. coli* 016 bladder infection. Treatment with cephaloglycin cleared the 016 bacteriuria, her introital cultures reverted to normal, and she has had no further infections in the six months since the 016 bacteriuria. Not only are her introital cultures devoid of any Gram-negative enterobacteria but copious fluid from the urethral diverticulum—obtained by urethral massage—is sterile.

before the 016 bacteriuria. The second exception is the last infection (*E. coli* 075) in Patient A, where (Table 1) 075 was not found on the introitus in the preceding culture, but this is the only patient in the ten whose male consort was

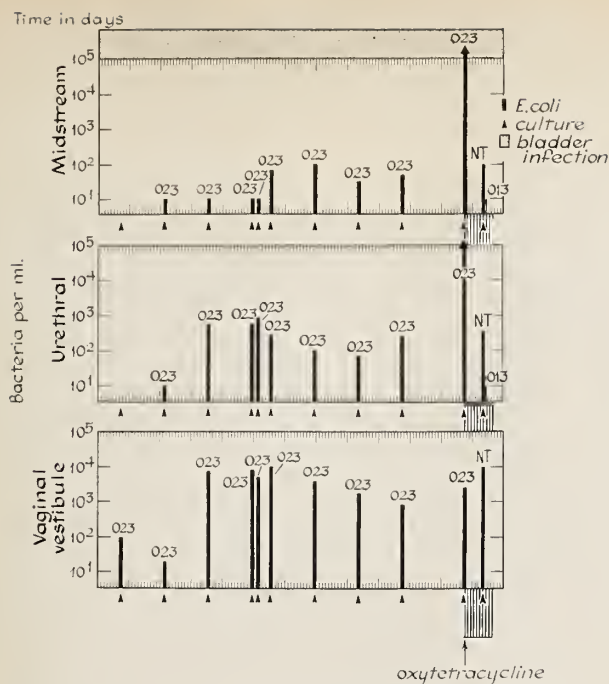


Chart 3.—Enterobacterial relationship of the vaginal vestibule, urethral, and midstream cultures in a 52-year-old, white, married woman (Patient H in Table 1). The only Gram-negative enterobacteria cultured were *E. coli*; the culture symbol (Δ), without overlying vertical bars, indicates the complete absence of Gram-negative enterobacteria. The serogroup of *E. coli* appears at the top of each solid bar; NT is a non-typable *E. coli*.

The patient's first urinary infection occurred two months after marriage, followed by only three infections in the next 25 years. A partial hysterectomy in 1966 was followed by multiple urinary infections. The *E. coli* 023 bladder infection illustrated in this chart was preceded by the constant presence of *E. coli* 023 on the introitus in pure culture, despite the fecal *E. coli* consisting of 91 percent *E. coli* 013, 5 percent *E. coli* NT, and only 4 percent *E. coli* 023.

shown to be a permanent carrier and the primary source of her urinary infections (both *P. mirabilis* 048 and *E. coli* 075).

The time elapse between permanent establishment on the introitus of the bacteria responsible for the next bladder infection and the occurrence of that infection varied between two and 151 days, with an average of 34 days (Table 1). The number of bacteria in the vestibule culture at the visit immediately preceding each bacteriuric episode is shown in Table 2, together with the time elapse between this last introital culture and the occurrence of the infection. With this one exception in Patient A, whose husband was the carrier for her infections, all bacteriuric episodes were preceded by large numbers of the infecting strain on the introitus.

TABLE 2.—Number of Infecting Organisms in the Vaginal Vestibule Specimen at Last Visit Before Bacteriuria

Patient	Organism	Days Between Bacteriuria and Preceding Culture	Bacteria per ml in Vestibule Culture
A	<i>Proteus mirabilis</i> 048	14	480
	<i>E. coli</i> 08	5	290
	<i>Proteus mirabilis</i> 048	9	80
	<i>Proteus mirabilis</i> 048	7	300
	<i>E. coli</i> 075	8	0°
B	<i>E. coli</i> 04	14	10,000
C	<i>E. coli</i> 04	7	10,000
D	<i>E. coli</i> 075	8	180†
	<i>E. coli</i> 075	14	10,000
	<i>E. coli</i> 075	8	4,100
E	<i>E. coli</i> 04	21	1,000†
	<i>E. coli</i> 016	2	80‡
F	<i>E. coli</i> NT	11	10,000
	<i>Proteus mirabilis</i> 010	14	100,000
G	<i>E. coli</i> 06	7	2,580
H	<i>E. coli</i> 023	21	860
	<i>E. coli</i> 023	13	1,510

Legend: *E. Coli* (08), etc.=0-antigen serogroup of *E. coli*.

NT=Non-typable *E. coli*.

P. mirabilis (048), etc.=0-antigen serogroup.

*An 075 was present on the vaginal vestibule in a culture 31 days before her 075 bacteriuria; this 075 *E. coli* was the predominant infecting strain of *E. coli* in her consort, who had chronic bacterial urethritis and possibly prostatitis.

†These cultures are urethral (first voided few ml) specimens; had the vaginal vestibule been cultured, the numbers would have been much greater.

‡Accompanied by 10^4 *E. coli* 04.

Interestingly, the infecting strain disappeared from the introitus at the time of the bacteriuria in two patients (Table 1, Patients F and G).

The Relation of pH and Hormonal Status of the Vaginal Vestibule to Recurrence of Bacteriuria:

The pH data in Table 1 show no consistent change in the vaginal vestibule either at the first detection of bacteriuria or at the preceding visit. The Papanicolaou stains of the vaginal vestibule smear and the membrane filter preparation of the urethral cells indicated no hormonal abnormalities; they were comparable in all respects to similar collections obtained from 30 women who had never had urinary infections.⁶

No evidence for an inflammatory reaction on the vaginal vestibule, as measured by the presence of polymorphonuclear leukocytes in either

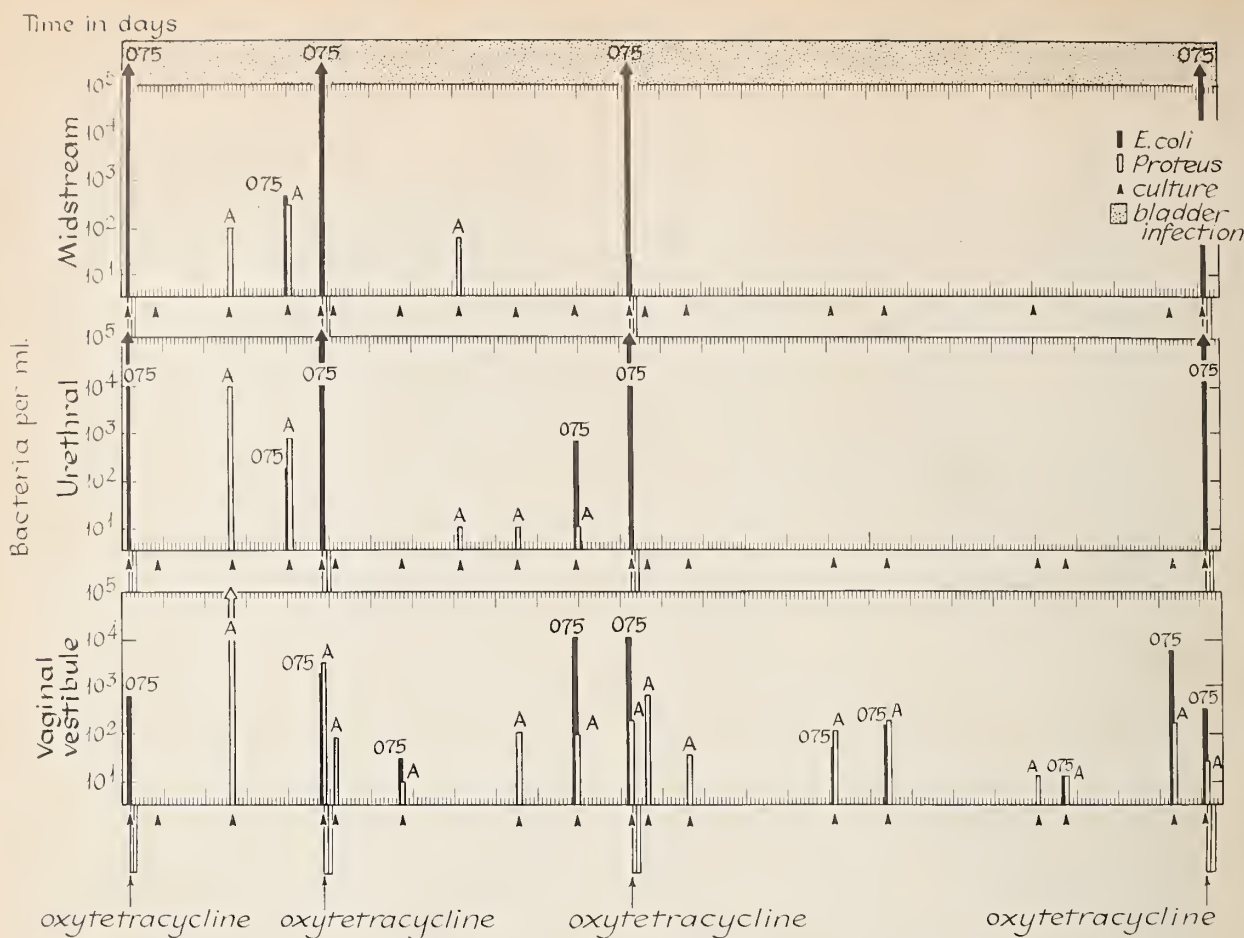


Chart 4.—Enterobacterial relationship of the vaginal vestibule, urethral, and midstream cultures in a 68-year-old, white, married woman (Patient D in Table 1) followed for eight months through four episodes of bacteriuria. All Gram-negative enterobacteria cultured are shown; the culture symbol (Δ), without overlying vertical bars, indicates the complete absence of Gram-negative enterobacteria. The serogroup of *E. coli* appears at the top of each solid bar. The open bars, *P. mirabilis*, with the symbol A, represent identical strains of *P. mirabilis* as shown by Dienes¹² swarming. Each strain has been serogrouped; all are 030.

All of the bacteriuric episodes in this case were caused by *E. coli* 075, but each one was preceded by large numbers on the introitus, thereby excluding the kidney as the cause of relapse. Although a vaginal vestibule culture was not obtained immediately preceding the second 075 bladder infection, the finding of several hundred *E. coli* 075 contaminating the urethral and midstream urine in the culture eight days before leaves no doubt of introital colonization.

The fecal *E. coli* serogrouped on two occasions, showed 80 to 100 percent *E. coli* 075. Oxytetracycline therapy for the bacteriuric episodes was limited to three days because of diarrhea associated with longer periods of treatment.

the fresh wet preparations or the Papanicolaou stains, could be detected.

The Relation of Mycoplasma And Anaerobic Bacteria to Recurrent Bacteriuria:

Despite frequent cultures for both T-strain Mycoplasma and Mycoplasma hominis, only Patient A had a positive culture on one occasion; two subsequent cultures from her were negative for mycoplasma.

Bacteroides species, by contrast, was cultured

from every patient at least one time, with the exception of Patient B, who was cultured only once for anaerobic bacteria. For example, Bacteroides species was found in three of ten cultures from Patient A, in two of five from Patient C, in two of twelve from Patient D, in one of eight from Patient E, one of fourteen from Patient F, six of fourteen from Patient G and two of four from Patient H. Colony counts of Bacteroides species, whether vaginal or urethral, varied between 100 and 1,500 organisms per ml of sample. Although further observations are needed, no consistent re-

lationship between the presence of *Bacteroides* and the establishment of aerobic enterobacteria on the vaginal vestibule could be detected.

Results of Cultures from Male Consorts:

All the patients were married, and seven of the eight women who had bacteriuric episodes during the time of these special studies agreed to bring in first morning voided specimens from their husbands. Four of the seven had the same serogroup of *E. coli* that was present in the vaginal vestibule of their wives (Patient A [075], Patient C [04], Patient E [04], and Patient G [06]). Except for the husband of Patient A and possibly of Patient G, these *E. coli* proved to be transient and could not be found on re-culture. As the husbands of Patients C, E and G were all circumcised, the pathogens were present on the urethra, not the foreskin. The 29-year-old, uncircumcised husband of Patient A, however, persistently carried large numbers of *E. coli* 075, *P. mirabilis* 048, and smaller numbers of *E. coli* 025 in his first voided aliquots. Upon examination, he was found to have an irregular firm prostate and a prostatic fluid loaded with inflammatory cells and chronic macrophages. Bacterial localization, using a method previously published,⁵ suggested the urethra and possibly the prostate as the source of his *E. coli* 075 and *P. mirabilis* 048. Not only were the serogroups of *E. coli* and *P. mirabilis* the same as in his wife, but his *P. mirabilis* swarmed readily with all three samples of *P. mirabilis* from her three episodes of bacteriuria. Finally, this husband had a history of one urinary infection in October 1968 ($>10^5$ *E. coli*) with a "negative" follow-up culture on 6 November 1968 three days after a five-day course of nalidixic acid therapy. Also he had had a single episode of left vas deferentitis in January 1968, treated with seven days of tetracycline.

The Introital Flora of the Two Patients Who Did Not Have Recurrence of Bacteriuria:

Patient K, who had documented episodes of *E. coli* bacteriuria on 24 May 1968 and 13 November 1969 (*E. coli* 073), had urine cultures 11 times in the first eight months of 1970. Eight of these cultures did not contain a single Gram-negative bacteria, one showed 100 *E. coli* per ml

(not serogrouped) and two showed ten *E. coli* per ml (serogroups 07 and 010). A further culture on 20 December 1970 also showed no enterobacteria. Her infections have ceased.

Patient J, a woman 20 years of age, had her first infection in April 1969 one month after starting sequential birth control estrogen. Interestingly, this infection occurred a few days after a gynecological premarital examination but before she began sexual intercourse. Her second bacteriuric episode was 23 January 1970 (*E. coli*). Nine cultures obtained between 18 February and 7 December 1970 showed Gram-negative bacteria on only two occasions (120 colonies of *E. coli* 012 per ml on 14 April and ten colonies of non-typable *E. coli* per ml on the introitus on 2 June). She became pregnant in April 1970 and delivered a full-term infant 14 December.

The Introital Flora of the Three Patients With a Single Bacteriuric Episode After Being Placed on the Study in 1970:

The bacteriologic course of Patient C is shown in Chart 1. After this paper was submitted for publication, ten consecutive specimens were obtained at 14-day intervals after the last culture shown in Chart 1. Except for *S. faecalis* and occasional, very small numbers of Gram-negative bacteria, the first seven introital cultures were not remarkable. The eighth culture, however, showed 20 colonies of *E. coli* 021 and 50 colonies of *E. coli* 04 per ml on the introitus, while the ninth culture had 910 colonies of *E. coli* 04 per ml on the introitus. Thirteen days after the ninth culture she was symptomatic with pyuria and 10^8 *E. coli* 04 per ml in the midstream urine. This second *E. coli* 04 bacteriuria occurring in Patient C, clearly preceded by the appearance of *E. coli* 04 on the introitus for the first time in six months, is not included among the 17 bacteriuric episodes in Table 1.

Patient F, whose first documented bacteriuria at Stanford occurred with an *E. coli* NT on 15 December 1969, had a single culture 11 days earlier that showed 10^4 *E. coli* on the vaginal vestibule, 5,000 *E. coli* per ml on the urethra and a sterile midstream urine. Following treatment with oral penicillin-G for the *E. coli* NT bacteriuria on 15 December, similar bacteria (*E. coli* NT) were present on the introitus in small numbers on 24 December 1969 and 11 March and 23

March 1970. On 27 March 1970, *P. mirabilis* 010 appeared on the introitus in 10^1 or greater per ml and persisted through four consecutive cultures until 1 June 1970, the date of her *P. mirabilis* 010 bacteriuria; the culture immediately preceding the bacteriuria was collected on 18 May 1970 (at which time she was mildly symptomatic) and showed the following: vaginal vestibule, *P. mirabilis* 010 10^5 per ml; urethral, 10^1 *P. mirabilis* 010 per ml; and midstream, 80 *P. mirabilis* 010 per ml. At the time of her bladder infection on 1 June 1970, *P. mirabilis* could not be cultured from the vaginal vestibule. Following ten days of oxytetracycline therapy, eight of the next ten cultures, including that of 4 November 1970, contained only non-typable *E. coli* on the introitus but in small numbers. Since 4 November she has had urine cultures eight times inclusive of 24 May 1971; except for the presence of *S. faecalis*, her introital cultures are similar to those of women who never have infections. It is interesting that her infections seem to have ceased without any change in sexual activities or social habits.

Patient G, who is 54 years old, had her first urinary infection in 1935 at the age of 20, a series of recurrences in 1942 and 1950, and intermittent episodes between 1950 and 1965. She was first seen at Stanford in April 1966. Urine cultures, including introital collections, were obtained on 26 visits between April 6, 1966 and 20 January 1970; three bacteriuric episodes, each one due to *E. coli*, were documented. Various courses of oral antibiotics, vaginal regimens, and post-intercourse antimicrobial agents all failed to prevent recurrent urethral symptoms when the bladder urine was sterile (urethral syndrome) as well as the occurrences of bacteriuria. The introital flora was almost always positive for large numbers of Gram-negative bacteria.

When she was placed in the present study on 20 January 1970, she stopped all antimicrobial agents as well as vaginal manipulations such as douching. The three cultures preceding her *E. coli* 06 bacteriuria on 10 April 1970 showed *E. coli* 06 on the vaginal vestibule (600, 3,300, and 2,580 per ml) with no other Gram-negative bacteria.

She was asymptomatic on 3 April 1970 at the time the vestibule showed 2,580 *E. coli* 06 per ml and the urethra 1,320 *E. coli* 06 per ml, and the midstream urine was sterile. Surprisingly, seven days later but only six hours after the onset of

urgency, dysuria, and left flank pain, the vaginal vestibule culture did not contain a single Gram-negative bacterium at a time when the urethral and midstream specimens contained $>10^6$ *E. coli* 06 per ml.

The bacteriuria due to *E. coli* 06 on 10 April 1970 was treated with ten days of oxytetracycline. Twenty-five cultures were obtained between 16 April 1970 and 7 April 1971. Except for two cultures, *E. coli* 06 has been present on every introital culture since the oxytetracycline therapy, usually in numbers less than 100 per ml but occasionally in the thousands. *S. faecalis*, *P. mirabilis*, *P. morgani*, and yeasts have often accompanied the *E. coli* 06. Urethral symptoms have occasionally been present, but without any apparent increase in the numbers of *E. coli* 06; no relationship between urethral symptoms and other pathogenic bacteria on the introitus have been established.

Influence of Antimicrobial Therapy for Bacteriuria on the Emergence of Gram-negative Enterobacteria On the Introitus:

Does antimicrobial therapy influence the emergence of Gram-negative pathogens on the introitus? The minimum inhibitory concentration (MIC) of several antimicrobial agents was determined for the first Gram-negative enterobacteria to appear on the introitus after initiation of therapy for a bacteriuric episode. Moreover, since the first bacteria to appear during or after treatment may not be the same pathogen that is ultimately established on the introitus and responsible for the next bacteriuria, we have also determined the MIC for these Gram-negative bacteria at the time of their first introital appearance. (All of these data, together with the sensitivity patterns of the organism in the bladder at the time of the bacteriuria, are available in a master chart, too large for publication here, which can be obtained by writing directly to the authors.)

Bacteria on the introitus that were sensitive before therapy developed resistance in only two of sixteen instances of antimicrobial treatment. In the first infection in Patient A (Chart 5), an *E. coli* 08 (MIC oxytetracycline 3 μ g per ml) was on the vaginal vestibule at the time of the *P. mirabilis* 048 bacteriuria. Although the *P. mirabilis* (MIC oxytetracycline >150 μ g per ml) was cleared

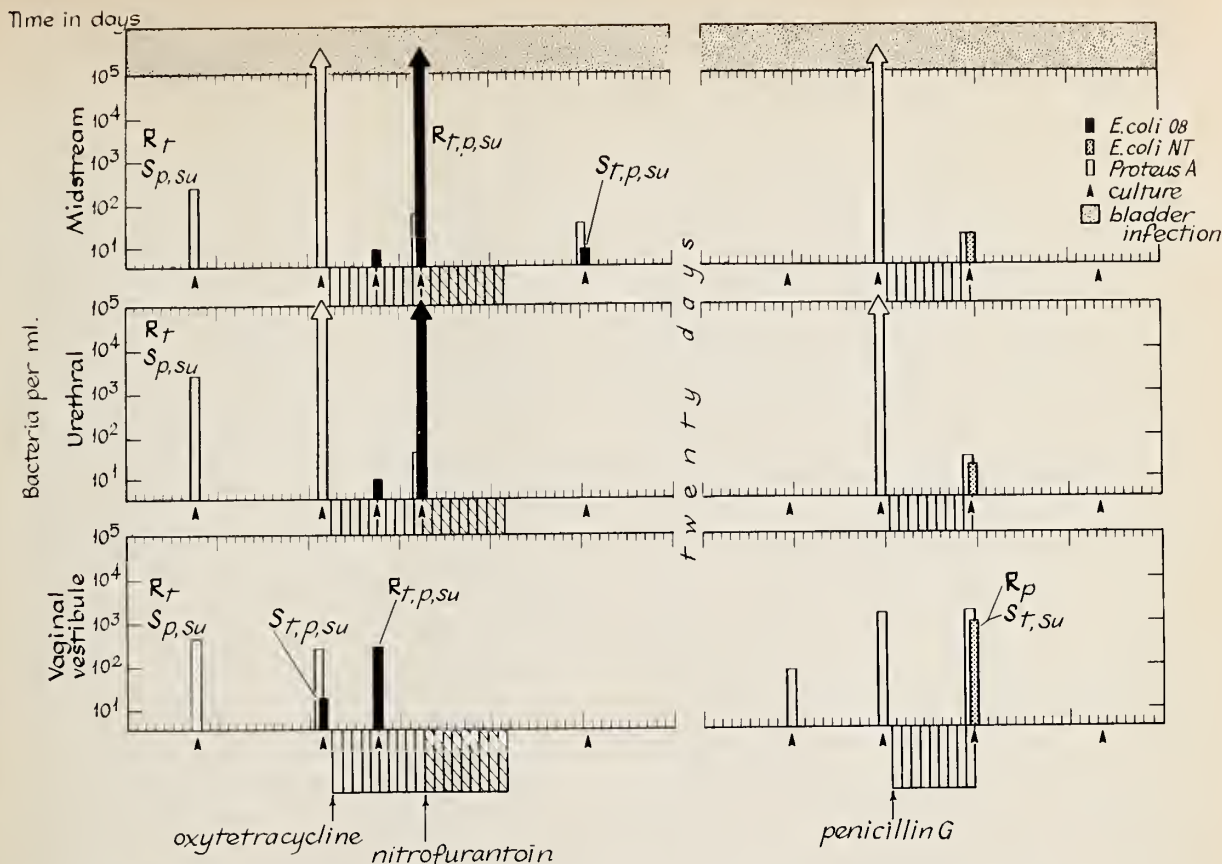


Chart 5.—Enterobacterial and antimicrobial relationship of the vaginal vestibule, urethral, and midstream cultures in a 27-year-old, white, married woman (Patient A in Table 1) with recurrent bladder infections. All Gram-negative enterobacteria cultured are shown, except for *Klebsiella pneumoniae* which appeared transiently in the introitus on four occasions: fewer than 20 per ml three times, and 4,000 per ml once; the culture symbol (Δ), without overlying vertical bars, indicates the complete absence of Gram-negative enterobacteria. *E. coli* 08 is indicated by the solid bars and *E. coli* NT (non-typable), appearing only once at the end of penicillin-G therapy, by the stippled bar. The open bars represent identical strains of *P. mirabilis*¹² swarming; all strains were found to be of the same 0-antigen serogroup (048). This *P. mirabilis* 048, resistant to oxytetracycline but sensitive to penicillin-G and sulfonamide, never changed its sensitivity. R=resistant, S=sensitive, t=oxytetracycline, p=penicillin-G, and su=sulfonamide.

The *E. coli* 08 bacteriuria, resistant to oxytetracycline, was selected from an *E. coli* 08 that was sensitive to oxytetracycline and present on the introitus before therapy. The simultaneous selection of resistance in the *E. coli* 08 to penicillin-G and sulfonamide in the presence of only oxytetracycline therapy, as well as the subsequent loss of resistance after stopping therapy, are characteristic of resistance transfer factors.

The transient appearance of resistant Gram-negative enterobacteria on the introitus following therapy, as seen in the *E. coli* NT present at the end of penicillin-G therapy, was common in this group of patients, but never of clinical significance.

from the urine by the fifth day of therapy, the *E. coli* 08 persisted on the introitus but was now resistant to oxytetracycline (MIC >150 μg per ml). Four days later, on the ninth day of oxytetracycline therapy, the *E. coli* 08 was in the bladder (Chart 5) and the patient was acutely symptomatic. Sensitive to nitrofurantoin (MIC 6 μg per ml), but maintaining resistance to oxytetracycline (MIC >150 μg per ml), this *E. coli* 08 bacteriuria was easily cleared with nitrofurantoin therapy; interestingly, the ten colonies per ml of *E. coli* 08 found in the midstream culture (but not in the

introitus) nine days after completing nitrofurantoin therapy (Chart 5) were still sensitive to nitrofurantoin (MIC 7 μg per ml) but had lost their resistance to oxytetracycline (MIC 3 μg per ml). The second example of resistance developing in the presence of previously sensitive bacteria was observed in Patient E (Table 1). The *E. coli* 04 present on the vestibule before her 04 bacteriuria was sensitive to oxytetracycline (3 μg per ml); seven days after therapy was begun, the *E. coli* 04 persisting on the vestibule was resistant (>150 μg per ml). In this case, however, unlike

Patient A, bacteriuria did not occur with the resistant strain. In fact, resistance of the *E. coli* 04 on the introitus was maintained for only four days after therapy; succeeding cultures showed reversion to a 2 µg per ml MIC of oxytetracycline for the introital *E. coli* 04. The oxytetracycline resistance that developed in the *E. coli* 08 in Patient A (Chart 5) and the *E. coli* 04 of Patient E carried a simultaneous resistance to sulfonamide (and to penicillin-G in Patient A) that was not present in the cultures before therapy (Chart 5). Since in subsequent cultures both the 08 and 04 strains lost their resistance to both oxytetracycline and sulfonamide, and since resistance to neither nitrofurantoin nor nalidixic acid developed in the post-treatment cultures, it is clear that these antimicrobial patterns were mediated by resistance transfer factors.¹⁶

A number of examples of resistant enterobacteria on the vestibule could be found following therapy, but these organisms were not cultured before treatment. Moreover, these resistant organisms either did not persist or soon lost their resistance. For example, the *E. coli* NT cultured from the vestibule in Patient B (Chart 2) five days after cephaloridine therapy was highly resistant (>1,450 µg per ml) to cephaloridine, but the *E. coli* 04 cultured on the same day was sensitive (2 µg per ml); the 04, however, persisted and caused the next bacteriuria (Chart 2). Further examples of resistant strains on the introitus after therapy include: (1) the *E. coli* NT resistant to penicillin-G (>1,170 µg per ml) in Patient A (Chart 5) at the end of penicillin-G therapy for the patient's second *P. mirabilis* 048 infection, and (2) the *E. coli* NT on the introitus in Patient C (Chart 1) present on the tenth day of sulfamethizole therapy (for the 04 bacteriuria), as well as the *E. coli* NT present 14 days after completion of therapy, were resistant to sulfamethizole (zero zone size); again these *E. coli* NT did not persist (Chart 1). Similar examples occurred in Patient F (Table 1) after oxytetracycline therapy (an *E. coli* NT resistant to >150 µg per ml), in Patient G after oxytetracycline therapy (a *P. mirabilis* 015 resistant to 128 µg per ml), and in Patient E after sulfamethizole treatment (an *E. coli* 06 resistant with zero zone size) as well as oxytetracycline therapy (a *P. mirabilis* 030 resistant to 108 µg per ml). All of these data are available in detail in the previously mentioned master chart obtainable upon request.

Discussion

The Relation Between Introital Enterobacteria and Bacteriuria:

These studies show that recurrent bacteriuria in the adult woman is preceded by the establishment of enterobacteria on the vaginal vestibule, and that large numbers are present just before the bacteriuric episode (an observation particularly obvious in Charts 1, 2, 3 and 4). The number of bacteria in the vestibule culture at the visit immediately preceding each episode of bacteriuria is shown in Table 2; the time elapse between this last introital culture and the bacteriuria is also indicated in the same table. If introital cultures had been obtained within 24 to 48 hours before the occurrence of each episode of bacteriuria, they might well have shown even more organisms; the logistics, however, of culturing asymptomatic women every two weeks proved difficult enough. Although Patient A (Chart 5 and Table 2) seems to be an exception, she is the only one whose consort provided inoculae numbering in the thousands of bacteria (*P. mirabilis* 048 and *E. coli* 075) originating from his urethral infection and accumulating in even greater numbers beneath an uncircumcised foreskin. Thus, sexual intercourse per se could provide enormous numbers of enterobacteria that need not have been present before sexual contact.

These observations, obtained without instrumentation of the urethra or bladder, establish that the microflora of the introitus determines the next recurrence of bacteriuria. Moreover, the flora of these women differs from that of women who never have infections in at least two respects: (1) the presence of large numbers of enterobacteria on the introitus, and (2) the persistence of a nearly uniform serogroup before the occurrence of bacteriuria. To fully appreciate this difference, the cultures reported here must be compared with similar ones from women who never have urinary infections.

When culturing of the urine of 30 premenopausal volunteers who had never had urinary infections or vaginitis was carried out with this technique, only four had enterobacteria on the vaginal vestibule and urethra: 550 *E. coli*, 120 *E. coli* (+10 *P. mirabilis*), 20 *E. coli*, and 10 *E. coli* per ml.⁶ Indeed, when re-culturing was done in the case of the volunteer with 550 *E. coli* per ml, no enterobacteria were found. Because this

TABLE 3.—*Enterobacteria in Five Normal Volunteers Cultured for Ten Consecutive Weeks*

Volunteers, Age and Site of Culture	E. Coli* per ml of Sample (and Serogroup)									
	1st week	2nd week	3rd week	4th week	5th week	6th week	7th week	8th week	9th week	10th week
1. 22 years old										
Vaginal vestibule	0	0	2250(04) 10(01)	10(01)	0	0	290(01)	0	0	880(01) 20(04)
Urethral	0	0	0	0	0	0	10(01)	0	0	0
Midstream	0	0	0	0	0	0	0	0	0	0
2. 30 years old										
Vaginal vestibule	0	0	0	0	0	0	0	0	0	0
Urethral	0	0	0	0	0	0	0	0	0	0
Midstream	0	0	0	0	0	0	0	0	0	0
3. 39 years old										
Vaginal vestibule	0	0	0	0	0	0	0	0	0	0
Urethral	0	0	0	0	0	0	0	0	0	0
Midstream	0	0	0	0	0	0	0	0	0	0
4. 34 years old										
Vaginal vestibule	0	0	0	0	0	0	0	0	0	0
Urethral	0	0	0	0	0	0	0	0	0	0
Midstream	0	0	0	0	0	0	0	0	0	0
5. 39 years old										
Vaginal vestibule	0	0	0	30(06)	0	0	0	0	0	2500(06)†
Urethral	0	0	0	10(06)	0	90(06)	0	0	0	100(06)
Midstream	10(06)	10(06)	0	30(06)	0	130(06)	0	0	0	50(06)

Legend: First number=the number of E. coli per ml in the specimen.
Number in ()=the O-serogroup of the E. coli.

*No Gram-negative enterobacteria, other than E. coli, was ever isolated from these cultures.

†Volunteer 5 could never void from the cystoscopy table and had to collect her own voided specimens; this accounts for the negative introital cultures but contaminated, low count voided specimens.

‡April 1, 15 days following tenth week culture, there were no E. coli on the introitus; a rectal culture showed the predominant serogroup was E. coli 010.

suggested that the normal introitus was only transiently colonized by low numbers of fecal bacteria, we studied five additional normal volunteers who agreed to have culturing done weekly for ten consecutive weeks (Table 3). Three volunteers did not have even one Gram-negative enterobacterium at any culture. The other two showed transient colonization but never in significant numbers (except for a single transient colony count of 2,250 E. coli 04 per ml on the vestibule of volunteer No. 1 and 2,500 E. coli 06 per ml in volunteer No. 5). *Proteus* species was not cultured once in these 150 specimens. *S. faecalis* was never cultured in our original studies on 30 premenopausal volunteers,⁶ but was con-

stantly isolated in the introital cultures of volunteers 4 and 5. We emphasize that no washing of the labia or introitus was done before the collection of either the vaginal or the voided cultures in these studies.

There is further evidence in these data to suggest a biologic difference in the introitus of women susceptible to recurrent infections. The microflora of the two patients (Patients J and K, Table 1, described in detail in the section titled "Results") who did not have a subsequent infection in the one year of observation after being placed on the study, is clearly similar to the volunteers who never have infections. This suggests that reversion to a microflora characterized by only

occasional enterobacteria in small numbers is tantamount to cessation of urinary infections.

Furthermore, the three patients with a single bacteriuric episode (Table 1) are interesting because of their long-term follow-up and frequent introital cultures. The introital cultures in Patient F, followed closely for 12 months since her *P. mirabilis* 010 infection (Table 1), soon reverted to normal and have remained so. Patient C, after her *E. coli* 04 bacteriuria in Chart 1, remained free of symptoms and infection for six months until the *E. coli* 04 reappeared on the introitus and four weeks later was in the bladder. Patient G, on the other hand, was almost never without *E. coli* 06 in her introital cultures in the 14 months following her *E. coli* 06 bacteriuria. She has repeatedly had urethral symptoms in the absence of bacteriuria. Two rectal cultures, serogrouping ten random colonies of *E. coli* each time, showed no 06 strains on one culture and 30 percent *E. coli* 06 on the second culture. Three cultures before and after urethral massage have not suggested the urethra as the site of persistence. Cervical and deep vaginal cultures have shown no *E. coli* when *E. coli* 06 are present on the vaginal vestibule. Six of seven cultures from her husband have shown an *E. coli* 06 in the urethral aliquot and usually in numbers of several thousand per ml. He, like the consort of Patient A, probably is the carrier of the *E. coli* 06 appearing in his wife.

The Absence of Enterobacteria on the Introitus at the Time of the Bacteriuria:

An unexpected observation was that two of the seven patients (Patients F and G, Table 1), after consistently carrying substantial numbers of *P. mirabilis* and *E. coli* 06, respectively, on the introitus before the occurrence of the bacteriuria, did not have a single culturable Gram-negative bacterium on the vaginal vestibule at the time of their bacteriuria. A woman normally wets her introitus with each micturition; hence, in the presence of bacteriuria, the very act of voiding should inoculate millions of enterobacteria onto the vaginal vestibule. How could the vaginal vestibule, previously characterized by large numbers of the organism responsible for the bladder infection, suddenly show none of these bacteria on culture in the presence of substantially increased exposure? To make sure these two instances were not artifacts, and since this technique of culturing the

female has been a routine in our laboratory since 1964, we reviewed the vaginal vestibule cultures from 37 consecutive women at the time of their presenting bacteriuria. None of them was receiving antimicrobial therapy. Twelve of the 37 did not have a single Gram-negative colony on the introitus at the time of the bacteriuria. The bacteriuria represented the first infection for three of the 12 women, but the remaining nine had had two or more infections in the preceding year.

These observations suggest local antibody stimulation by the occurrence of the bacteriuria. Serial studies relating vaginal vestibule antibody to the persistence of enterobacteria on the introitus, their disappearance in a third of our patients at the time of the bacteriuria, and the possible relationship of local antibody to the selection of the next enterobacteria to become established on the vestibule, are under way. Although serum antibody studies have failed to explain or correlate with susceptibility of patients to urinary infections,¹⁷ our observations suggest that a study of local antibody on the introitus in relation to the persistence of enterobacteria might be rewarding.

The Fecal Reservoir:

We have not examined the fecal reservoir serially in these patients because other investigators have established that the organism causing the bacteriuria can be found in rectal swabs from 70 to 80 percent of the time,^{2,3} and because of the large sample size of fecal bacteria that would have to be examined¹⁸ in order to conclusively exclude the intestines as the ultimate reservoir in the 20 to 30 percent where identity might not occur.

For example, Kennedy et al found that 11 of 17 *E. coli* infections in the urine of patients in hospital were associated with carriage of the identical strain in the stool, but in the remaining six instances the strain could not be detected even though an additional 100 colonies per stool culture were examined.¹⁹ On the other hand Grüneberg et al, in a study of urinary infections from domiciliary practice, found only one of twenty-three patients who did not have the infecting strain on the rectal swab. In fact, from serogrouping only ten fecal colonies from each patient, they found the infecting strain to correlate with the majority (five or more) of the rectal colonies in 19 of the 23 patients.⁴ Clearly, fecal *E. coli* are the ultimate reservoir for enteric urinary infections. But since this reservoir is similar in women from the same

community who are not susceptible to urinary infections,⁴ we believe the difference—and therefore the characterization of susceptibility—lies in the colonization and growth to large numbers of enterobacteria on the vaginal vestibule. In the presence of many bacteria on the vaginal vestibule, our cultures both from normal women⁶ and those with recurrent infections presented in this paper are convincing that the urethral flora is determined by the introital bacteria.

Since normal feces are known to contain a "resident" flora consisting of one or two dominant strains of *E. coli* that persist for long periods, and a "transient" flora present for a much shorter time,²⁰⁻²² it is likely that establishment and persistence on the introitus of strains only transiently present in the fecal flora explains the 20 to 30 percent failure to always find the bacteriuric organism in the fecal reservoir. A similar conclusion was reached by Lincoln et al, who observed persistence of an *E. coli* in the urethra of a male infant when the *E. coli* could not be found in the stool.²³ Our occasional examinations of the fecal *E. coli* in these ten patients have served to convince us of the primacy of the introitus. For example, although the introital *E. coli* 075 in Patient D (Chart 4) is clearly related to her fecal reservoir, the persistent introital *E. coli* 06 in Patient G (Table 1) could not be found among the fecal *E. coli* on one examination. Moreover, in Patient H (Chart 3), *E. coli* 023 is always present on the introitus in pure culture, but this *E. coli* constituted only 4 percent of the fecal *E. coli* in this patient on one study and could not be found in the second rectal culture. Patient A (Chart 5) has neither *P. mirabilis* nor *E. coli* 075 in her rectal reservoir, but her husband's urethra and uncircumcised foreskin represents the carrier site for her infections. These observations have convinced us that the bacteriologic status of the introitus—not the intestine—determines urinary infections.

The Problem of "Relapse":

The practice of dividing recurrent urinary infections into reinfections and relapses has been useful in that it has emphasized that about 80 percent of recurrences in children^{24,25} and adults²⁶ are reinfections. But many investigators have used *relapse* to imply that the site of the persistence is in the kidney.²⁷ Just as we have shown in the male that persistence is from the prostate and not

the kidney,⁵ the data here show that relapse in women without infection stones or azotemia can occur from the introitus and not the kidney. Patient D in Table 1 (see also Chart 4) had four bacteriuric episodes, all due to *E. coli* 075, in 1970; fortunately, the bacteria from her infections in 1965 and 1966 had been banked and were found to be *E. coli* 075. Thus, she is an excellent example of long-term relapsing infections, with all six bacteriuric episodes in her case having been caused by *E. coli* 075. However, her introital bacteria have been cultured and saved regularly since April 1970; all three infections were preceded by the establishment of large numbers of *E. coli* 075 on the vaginal vestibule. A urethral focus might be considered as the cause of her relapses, but repeated attempts to massage *E. coli* 075 from the urethra have met with failure. Furthermore, several cultures (Chart 4) show *E. coli* 075 on the vaginal vestibule at a time when none of these organisms were on the urethral mucosa. Rectal cultures, obtained with an anal speculum, showed 100 percent of the fecal *E. coli* flora to be 075 on one occasion, and on a second culture 80 percent were 075 and 20 percent were non-typable. The same strain of *P. mirabilis* 030 (Chart 4) was also cultured from the rectal reservoir.

The three relapses with identical strains of *P. mirabilis* in Patient A not only came from the introitus (Table 1) rather than the kidney, but were secondary to the husband's bacterial urethritis. This patient's one episode of *E. coli* 08 bacteriuria was selected from the introitus by antimicrobial therapy (Chart 5), and her last infection with *E. coli* 075 was the predominant coliform strain accompanying her husband's *P. mirabilis* 048 urethritis. The Dienes phenomenon of swarming¹² was checked for each strain recovered from the introitus, from colonies representative of each bacteriuria, and from the strains of *P. mirabilis* recovered from the husband's cultures. All strains showed identity by complete swarming. Krikler, comparing the Dienes phenomenon with specific proteus antisera, concluded that Dienes swarming, with minor exceptions, was even more specific than somatic antigen typing for demonstrating differences between strains.²⁸ Dr. Norman A. Hinton, Professor and Chairman of the Department of Bacteriology, University of Toronto, serogrouped all our isolates of *P. mirabilis* from these patients. Isolates from the same patient that swarmed together were always of the same O-anti-

gen serogroup, and isolates from different patients that repelled each other in the swarming test were always of different O-antigen serogroups. But swarming together in the Dienes test often occurred in strains from different patients with *P. mirabilis* of different O-antigen serogroups. Storey used the Dienes test to show an 83 percent correlation between infecting strains of proteus and the rectal reservoir in patients in hospital;²⁹ urinary infections provided the majority of strains. Krikler considered the incidence of proteus in normal feces to be about 27 percent.²⁸

Further examples of consecutive bacteriuric episodes of the same serotype, clearly caused by reinfection from the introitus, include the recent *E. coli* 04 bacteriuria of Patient C, a bacteriuria that occurred six months after the last one shown in Chart 1. Patient H, following completion of oxytetracycline therapy for her *E. coli* 023 bacteriuria (Chart 3), reestablished the *E. coli* 023 on her introitus by the second culture. In the next eight consecutive cultures, *E. coli* 023 was again present on the introitus in large numbers similar to Chart 3. Bacteriuria, due to *E. coli* 023, occurred on the ninth culture (13 May 1971), Table 1. Thus, of the 18 bacteriuric episodes analyzed in this paper, five of the consecutive infections (Patients A, C, D and H) were of the same O-serogroup, but each recurrence was caused by reinfection from the introitus.

These studies suggest that "relapse" cannot be considered as evidence of persistent renal infection unless introital cultures can be shown to be free of the responsible pathogen immediately before the bacteriuria. The observation that long-term therapy for "relapsing" infections may be more beneficial than short-term therapy, as maintained by Turck et al,³⁰ need not be related to curing persistence in the kidney; long-term therapy, compared with shorter periods of treatment, may simply allow the introital bacteria to return to normal.

The Influence of Antimicrobial Therapy On Introital Enterobacteria:

We expected to find that antimicrobial therapy played an important role in the selection of enterobacteria on the introitus, but only once (Chart 5) did this selection prove to be of clinical significance. However, because of a concurrent but unrelated study, oxytetracycline is the only antibiotic used frequently enough in these 17 bacteriuric

episodes to draw any conclusions, and therapy was deliberately limited to short courses of ten days each. Different antimicrobial agents and longer periods of therapy may lead to different conclusions. But within these limitations, bacteria on the introitus that were sensitive before therapy, developed resistance in only two instances of antimicrobial therapy (both with oxytetracycline therapy). In one (the *E. coli* 08 in Patient A, Chart 5), bacteriuria occurred immediately with the resistant strain, but in the other (an *E. coli* 04 in Patient E) it did not. Resistance was mediated by transfer factor in both these *E. coli*, and it was promptly lost within a few days of stopping therapy. Seven instances of antimicrobial resistance occurred in bacteria on the introitus after the initiation of therapy, but none of these organisms were present before treatment; in only one of the seven was the resistance pattern suggestive of transfer factor. In every case, either the introital strain lost its resistance after stopping therapy or else it did not persist on the introitus. Thus, in this small series, antibiotic resistance was readily demonstrated in the introital bacteria after initiation of therapy, but it was rarely of clinical significance. Nevertheless, this is clearly a neglected but important aspect in the evaluation of antimicrobial usefulness.

Lincoln et al showed that following ten days of therapy for sulfonamide sensitive urinary infections in eight infants, five were reinfected with sulfonamide resistant *E. coli* that appeared first as a resistant flora in the feces.²³ They concluded that "the fecal changes preceded reinfection and determined the bacteriology of the recurrence." They also suggested that it was important to study the effects of individual antibiotics on the fecal flora. Our studies reported here establish that virtually every recurrence of bacteriuria in adult women is preceded by the presence of enterobacteria on the introitus. It would be useful to know if antimicrobial therapy, in women who are not susceptible to urinary infections, changes the normal introital flora to one in which enterobacteria become established in substantial numbers.

The Role of pH, Hormonal Status, Mycoplasma, Anaerobic Bacteria And S. Faecalis:

To the extent that these observations suggest a biologic difference in the introitus of women sus-

ceptible to recurrent urinary infections, what is the basis of this difference? Ecologic factors such as mycoplasma and anaerobic bacteria (species of bacteroides) might allow enterobacteria to flourish on the introitus. Our studies exclude T-strain Mycoplasma and Mycoplasma hominis as ecologic influences; anaerobic bacteria on the introitus are probably unimportant, too, but further observations are needed.

The pH and hormonal status of the introitus, as estimated by nitrazine paper and Papanicolaou smears, appear the same as measurements from our study of 30 normal volunteers.⁶ Moreover, we can find no sign of an inflammatory reaction on the introitus as represented by leukocytes.

S. faecalis, on the other hand, may be important. All the women who had infections in this study carried *S. faecalis* on the introitus in at least 50 percent of their cultures, whereas our normal controls were rarely observed to be colonized.⁶ Moreover, we have noted that *S. faecalis* inhibits the *Lactobacillus* organism.

The Significance of the Male Consort Cultures:

We were surprised that four out of seven male consorts had the same *E. coli* serogroup on their urethral mucosa as was present in the vaginal introitus of their sexual partners. Since only random cultures were made of the males, it is likely that this is even more common. In two of the four males, colonization was transient, but the husband of Patient A (Table 1) had bacterial urethritis, was uncircumcised, and was clearly playing a major role in his wife's infections. Following the *E. coli* 075 bacteriuria of Patient A, sexual contact, except with condom, was prevented for 90 days. The husband was treated for ten days with cephalixin; during treatment, all his localization cultures (including swabs of the inner surface of the foreskin) were sterile, but after stopping therapy he promptly had relapse with the same strain of *P. mirabilis* 048 and the *E. coli* 075 in his urethral and foreskin cultures. Several other antimicrobial regimens met with equal failure. During the same period of avoiding sexual contact, Patient A was cultured at weekly intervals. Her introital cultures promptly reverted to normal; and five consecutive cultures did not show a single Gram-negative enterobacteria on the introitus. The husband of Patient A was circumcised on 25 March 1971; all his cul-

tures promptly reverted to normal. The last three cultures have shown no Gram-negative bacteria in the urethra. These studies clearly establish the primary role of the husband in the genesis of this patient's pathogenic introital flora and her recurrent bacteriuria.

For most patients, however, transient colonization of the male urethra with pathogenic enterobacteria probably has more significance for the male than the female; it could offer one explanation of how enterobacteria become established in the male prostate.⁵

Concluding Remarks

Following our report in 1967 that the introital bacteria of women resistant to urinary infections was substantially different from the flora in women who have recurrent infections,⁷ two recent publications have appeared in the British literature. Grüneberg cultured the vaginal and periurethral areas (exact method not described) with moistened cotton-wool swabs at the same time he cultured the rectum and urine at the time of the bacteriuria. He found the average frequency of the urinary serogroup in the rectal flora was 80 percent, in the vaginal flora 90 percent, and in the periurethral "skin flora" 93 percent;³¹ Vosti et al reported 80 percent identity of paired specimens with the rectal flora and 92 percent with the vaginal flora at the time of the bacteriuria.³ In eight patients, rectal, vaginal and periurethral swabs were collected by Grüneberg at two and six weeks after therapy. He observed persistence of the urinary organism in the perineal carrier sites in seven of the eight patients, but observations were not extended beyond the six-week culture. In only two patients were the carrier sites cultured (once each) before the occurrence of bacteriuria; apparently the urinary strain was found in the rectal culture of one patient (not, however, in the vaginal or periurethral areas), but in none of the carrier sites of the other (time lapse between culture and bacteriuria is not stated).

More recently, O'Grady et al³² examined the carriage of enterobacteria in the introitus of "normal" women and in patients presenting with the "urethral syndrome"—symptoms suggestive of urinary infection without bacteriuria. From a single swab examination, these investigators observed no difference in the prevalence of introital enterobacteria in normal compared with symptomatic

women who had the urethral syndrome. Urinary infection developed in 57 percent of 122 women with the urethral syndrome, but a detailed analysis of the introital flora before the occurrence of the bacteriuria is not given. Nevertheless, only three out of sixteen persistent carriers of enterobacteria on the introitus (numbers of bacteria not stated) remained uninfected while in half the 28 "non-carriers" infection did not develop. From our own observations, and clearly apparent in Charts 1 to 4, the definition of a "non-carrier" depends upon the frequency of observation and especially the proximity of the cultures to the period immediately preceding the occurrence of the bacteriuria. Moreover, analysis of Charts 1 to 4 shows there were sporadic cultures where no enterobacteria could be detected on the vaginal vestibule, urethral, or midstream specimens. In general, these occurred soon after therapy, as seen in Chart 2 following both cephaloridine and oxytetracycline therapy. Patient D (Chart 4) usually had at least a 20- to 30-day period following each course of therapy for her *E. coli* 075 bacteriuria when no *E. coli* 075 could be cultured in any of the specimens.

We have no explanation as to why a single strain of *P. mirabilis* 030, almost constantly present in all Patient D's cultures (Chart 4), never caused bacteriuria; why was it always the *E. coli* 075 that reached the bladder when the *P. mirabilis* 030 often had precedence? Could the search for an explanation as to why *E. coli* serogroups 04, 06, and 075 cause urinary infection with greater frequency than other serogroups of *E. coli*^{3,4,19} be related to a greater propensity of these strains to multiply on the vaginal vestibule?

In addition to these studies by Grüneberg³¹ and O'Grady et al,³² other investigators have attempted to study the urethral flora by a variety of methods, all of which involve some kind of instrumentation of the urethra.^{33,34} This has the disadvantage in longitudinal studies on women, with recurrent infections, of introducing urethral bacteria into the bladder urine and thereby preventing a study of the patient's natural history. This undoubtedly occurred in the eight patients reported by Cox et al where a modification of the Helmholtz cot was introduced 4 cm into the female urethra.³³ These previous studies, however, are open to the more serious criticism that the urethral cultures of the control subjects, with which the urethral flora of women with recurrent infections

was compared, did not represent a truly control population of women known to be free of urinary tract disease or recent antibiotic ingestion. For example, in the study by Cox,³⁴ all of his controls had hospital history numbers, some had dysuria, and 10 percent grew *Aerobacter aerogenes* in the urethral cultures, an organism we have never found once in over 70 adult women with negative history for urinary infections who have volunteered for cultures. The selection of controls from a "well-woman's" clinic, as well as surgical and medical outpatient clinics, is also of some concern in the paper by O'Grady et al;³² moreover, it is probably important to carefully exclude volunteers with a recent history of antibiotic ingestion, and the attendance at clinics makes this less likely.

These differences in the careful selection of volunteer women who have never had urinary infections are important. For example, Cox³³ concluded that "the non-infected state of the normal bladder was maintained largely by its natural resistance rather than by a lack of available pathogens." Our data lead us to the opposite conclusion: (1) that the introitus of the normal premenopausal woman is rarely colonized, and then only transiently, with small numbers of enterobacteria; and (2) that the primary incident in the chain of events leading to bladder bacteriuria is the establishment of a pathologic flora on the introitus and its subsequent growth to substantial numbers before causing the bacteriuria.

Acknowledgement: The authors express their great debt to Mrs. Yvonne Lowery, RN, who patiently collected these hundreds of specimens, to Dr. Norman A. Hinton, Professor and Chairman, Department of Bacteriology, University of Toronto, who serogrouped all our strains of *P. mirabilis*, and to Dr. Kenneth L. Vosti, Associate Professor of Medicine, Stanford University, for his detailed instructions and training in serogrouping the *E. coli*.

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A CHANGED VIEW OF HYPERPARATHYROIDISM

"Hyperparathyroidism exists in about 1 in 1,000 adult patients coming to the usual medical clinic. . . . With such a vast number of patients with the disease and such vast numbers being seen with the aid of the autoanalyzer, it's been necessary for us to change our minds materially on what to do surgically about hyperparathyroidism. In the past we've largely made the diagnosis on complications of the disease, and there's no question that patients with such complications should still be operated upon. However, if the patient has 'chemical' hyperparathyroidism with no complications or has had a kidney stone years back but now has no evident activity, our policy is to wait and watch; we no longer operate on the basis of a chemical diagnosis alone. I would add that this is by no means a final solution. No one has ever followed proven cases of hyperparathyroidism without complications for indefinite periods, and we don't know what's to happen to them. If they begin to get into trouble, we shall have to revise our current opinion."

—B. MARDEN BLACK, M.D., Rochester
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Therapeutic Abortions

A Review of 567 Cases

PAUL H. BRENNER, M.D., EDWARD J. KIRSCHEN, M.D., AND
JOSEPH M. DIDIO, M.D., *San Diego*

■ *Five hundred sixty-seven therapeutic abortions have been reviewed at the University Hospital of San Diego County. The primary source of referral was through local counseling agencies within the area. Most of the patients were unmarried primigravidas between the ages of 15 and 24. Increases in complications, in length of stay in hospital and in cost were directly related to delay in obtaining an abortion. The maximum psychological impact was felt before admission and at the time of discharge. It is felt that programs must be devised which are moral, ethical and efficacious and which serve not only to help the patient obtain an abortion within the first trimester but also to assist, direct and educate that stressed patient in need.*

ON NOVEMBER 8, 1967, the California statute concerning abortions became effective. It permits abortion under two general provisions: (1) when "there is substantial risk that continuance of the pregnancy would gravely impair the physical or mental health of the mother" and (2) when "the pregnancy resulted from rape or incest." It further requires that the abortion be performed by a licensed physician, in a hospital accredited by the Joint Commission on Accreditation of Hospitals, and only after approval by a committee of the hospital's medical staff. There is no residency restriction and there are no provisions as to fetal indications for termination of pregnancy.¹ Repeals of abortion acts in Hawaii, District of Columbia, Colorado and New York have heralded demands for similar changes in other states.

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In California in 1968, an average of 15 therapeutic abortions for each 1,000 live births were performed (5030 abortions, 339,323 live births). During the first nine months of 1969, there were 35 abortions per 1,000 live births, more than twice the rate of the previous year (9169 abortions, 264,750 live births). With abortion law reform or repeal, this ratio appears to be increasing rapidly. However, 35 abortions per 1,000 live births is still lower than the ratio found in other countries with established liberal abortion laws, namely, Sweden (ratio of 51 per 1,000 live births), Denmark (60 per 1,000), Finland (61 per 1,000) and decidedly lower than Japan (912 per 1,000), Czechoslovakia (344 per 1,000) and Hungary (1,356 per 1,000).² Applying the rates developed by Abernathy et al³ to the California population, estimates of total abortions for the state in 1968 were calculated to be 81,600—more than 76,600 of them illegal. This suggests that therapeutic abortions were approximately

six percent of California's total induced abortions in 1968, and about 12 percent of the total in 1969.

To cope with the problem of abortion on request, it is essential that adequate programs be devised prospectively to manage the logistics of hospital and operating room time and to be prepared to treat the postabortal mental stresses. To this end, we have analyzed our experiences with therapeutic abortions performed at University Hospital of San Diego County, and this analysis serves as the basis for this report.

Material and Method

This study consists of 567 consecutive therapeutic abortions performed at the University Hospital of San Diego County between December 1967 and December 1969. Data on patients aborted in that time were obtained by chart review and, when necessary, by communication with the attending physician. Each case was reviewed for the following factors: patient status (private or clinic), indication for therapeutic abortion, age at time of abortion, marital status, race, number of pregnancies, method of payment, type of abortion done, length of stay in hospital, length of gestation at time of abortion, total fluid loss (estimated or measured for dilatation and curettage only), operative and post-operative complications, and follow-up.

The applicant for therapeutic abortion was first seen by the obstetrician-gynecologist for confirmation of pregnancy. She was then referred to either a psychiatrist, internist or the district attorney, depending on the indication for abortion. The case was then presented to the Therapeutic Abortion Committee of the University Hospital of San Diego County, which consists of two obstetrician-gynecologists, two psychiatrists and an internist. The average time between the patient's visit to the obstetrician-gynecologist and admission for abortion was two weeks.

Three basic procedures were utilized for therapeutic abortion:

1. *Dilatation and suction curettage.* This was performed on all patients of 13 weeks' gestation or less and in approximately 50 percent of all patients at 14 weeks' gestation. All patients were admitted to hospital and taken to surgery the following day. Anesthesia was by intravenous thiopental, followed by light nitrous oxide and

oxygen inhalation anesthesia. After examination under anesthesia, the uterine cavity was sounded and the cervix was progressively dilated with either Hanks or Pratt dilators. (In a few cases the Vibrodilator^o was employed, but repeated difficulties, to be described, ultimately led to abandonment of this technique.) Evacuation of the products of conception was then effected by the use of a high vacuum, high capacity pump connected to a suction curette.^o The products of conception were inspected and forwarded for histologic review after termination of the procedure. In all cases between December 1967 and September 1969, the blood loss was estimated by the physician. Between October 1 and the end of December 1969, this was accomplished by the calibrated collection bottle measurement on the suction apparatus.

2. *Amniocentesis followed by intra-amniotic injection of hypertonic saline solution.* This method was employed in 76.5 percent of all patients over 14 weeks' gestation. In most instances it was delayed until 16 weeks' gestational size to facilitate ease of procedure. The patient was brought to the ward examining room and intravenous 5 percent dextrose in water started. Patients were given intravenous diazepam (Valium[®]) 10 mg. After lower abdominal preparation with povidone-iodine (Betadine[®]) solution, local anesthesia was employed, using lidocaine injection. A No. 16 needle containing a thin metal obturator and jacketed by a teflon catheter was then introduced through the anterior abdominal wall into the amniotic sac. The obturator was removed to ascertain free flow of amniotic fluid, after which the needle was removed, leaving only the catheter in place. The amniotic fluid was allowed to exit freely via the catheter without aspiration. Fifteen to 200 ml of amniotic fluid were removed, followed by slow injection of 150 to 200 ml of 20 percent sterile saline solution. The patient was observed closely during and after the procedure and was returned to her room. Intravenous fluids were continued, and if labor did not ensue within 10 hours, oxytocin (20 units per liter of 5 percent dextrose in water) was started.

3. *Primary hysterotomy or hysterectomy.* This was performed in 23.5 percent of all patients of 14 weeks' gestation or more. It was selected

^oBerkeley Tonometer Co.
Berkeley, California

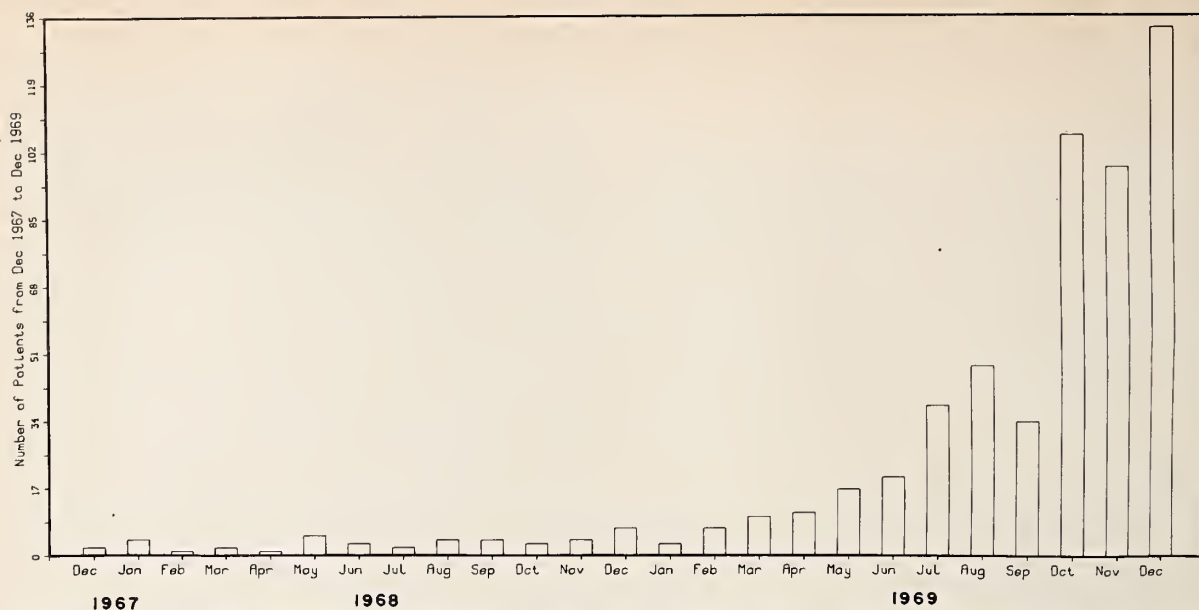


Chart 1.—Growing incidence of therapeutic abortions in period 1967-1969 at University Hospital of San Diego County.

either because of personal preference on the part of the attending physician or because of the desire of concomitant sterilization by the patient. In a number of cases in which the intra-amniotic injection of saline solution failed to result in passage of the fetus, a secondary hysterotomy or hysterectomy was performed.

Results

Type of Abortions Performed

Of 567 abortions, 431 (76 percent) were performed by dilatation and curettage, 104 (18.3 percent) by hypertonic saline solution injection, and 32 (5.7 percent) by primary hysterotomy or hysterectomy.

Demographic Factors

Incidence. During the period under review, the number of cases per month steadily increased, with significant rises noted in late spring and autumn of 1969 (Chart 1).

Patient Status. Of the patients treated, 480 (84.6 percent) were attended by private physicians and 87 (15.4 percent) were referred from the gynecology clinic. From December 1967 through December 1968, the proportion of private patients was 61 percent. During the first eight months of 1969 this rose to 82 percent, and for the last four months of the study 89 percent of all patients who had abortions were private.

Indication. The vast majority of procedures (549 or 97.0 percent) were performed for mental health of the patient, only eight cases (1.3 percent) for medical indication and 10 cases (1.7 percent) for rape or incest.

Age. As to age distribution of the 567 patients, nine (2.3 percent) were under 15 years, 177 (31.2 percent) were 15 to 19, 297 (51.8 percent) were 20 to 29, 73 (12 percent) were 30 to 39 and 11 (2.7 percent) were 40 and over.

Marital Status. Single patients (never married) accounted for 369 or 65 percent of the total group. Patients already married at the time of abortion accounted for 94 or 16.5 percent and the category listed as "other"—that is, widowed, separated or divorced—accounted for 104 or 18.5 percent. Unmarried patients made up 45 percent of the group from December 1967 through December 1968. This proportion rose to 58 percent for the first eight months of 1969 and in the last four months of the study to 70 percent. During the same periods, the married patients accounted for 21 percent, 25 percent and 13 percent respectively.

Race. Of the total population studied, 525 (92.5 percent) were Caucasian, 25 (4.4 percent) were Negro and 17 (3.1 percent) were "other," mainly Mexican-American. For comparison, the last 567 obstetrical deliveries performed at this hospital were distributed as follows: Caucasian

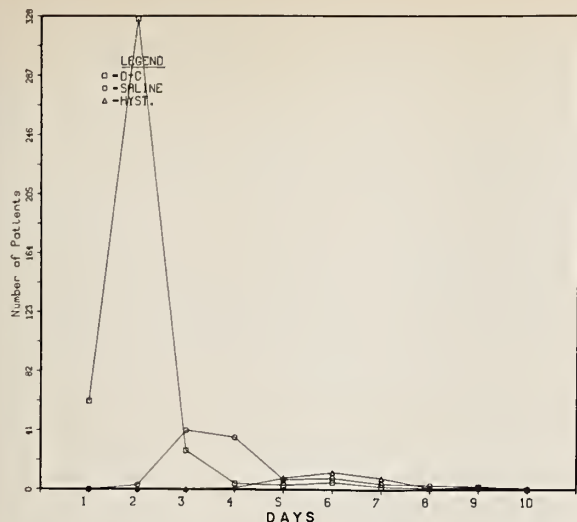


Chart 2.—Length of stay in hospital for therapeutic abortion in relation to method used.

40.1 percent, Negro 8.2 percent and "other" (again mainly Mexican-American) 51.7 percent.

Number of Pregnancies. Of the 567 patients, 328 (57.8 percent) were primigravidas; 144 (25.4 percent) were gravida 2 or 3; and 95 (16.8 percent) were gravida 4 or more.

Method of Payment. Title 19 (Medi-Cal) subsidized care in 247 or 43.5 percent; individual private payment accounted for 209 (36.8 percent); unknown payment type (as shown in the official log) 104 (18.4 percent); "Other" was seven (1.3 percent). In no case did private plan insurance pay for the procedure.

Factors Related to Delay Between Diagnosis and Termination of Pregnancy

Duration of Time in Hospital. The majority (75 percent) of patients who had dilatation and curettage were inpatients for 48 hours. Seventy-five percent of those aborted by saline solution inductions were in hospital three to four days, while in those undergoing hysterotomy or hysterectomy, 52 percent were in hospital for five to six days and 38 percent for seven or more days (Chart 2). No significant correlation was found between duration of hospital stay and age. In comparing duration of hospital stay to uterine size at the time of abortion, it was noted that there was a significantly longer stay for patients 14 weeks or more in gestation, probably related to the increased number requiring hysterotomy or hysterectomy.

Duration of Gestation at Time of Abortion.

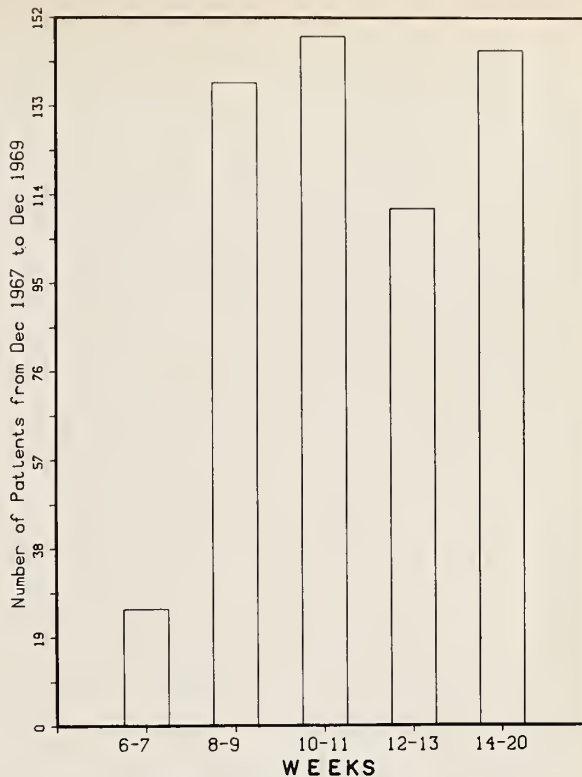


Chart 3.—Data on number of weeks of gestation (as determined by uterine size) at time of abortion.

Uterine size estimated by physical examination at the time of abortion (and stated in terms of estimated weeks of gestation) is shown in Chart 3. Twenty-five patients (4.4 percent) were six to seven weeks; 138 (24.3 percent) were eight to nine weeks; 148 (26.1 percent) were 10 to 11 weeks; 111 (19.5 percent) were 12 to 13 weeks and 145 (25.7 percent) were 14 to 20 weeks. When duration of gestation was matched with patient age, it was found that patients 30 to 39 years of age came to abortion earliest, followed by those 20 to 29, then 15 to 19, and lastly, those under 15. When duration of gestation was related to type of payment, it was apparent that the patient who requires Medi-Cal application and processing to finance her procedure is admitted to hospital later than the private-paying patient, while patients already on Medi-Cal at the time of conception enter earlier.

Fluid Losses Associated With Dilatation and Curettage for Abortion

There are no accurate, reproducible means of separating and calculating amniotic fluid volume for early gestation. Between six and 11 weeks,

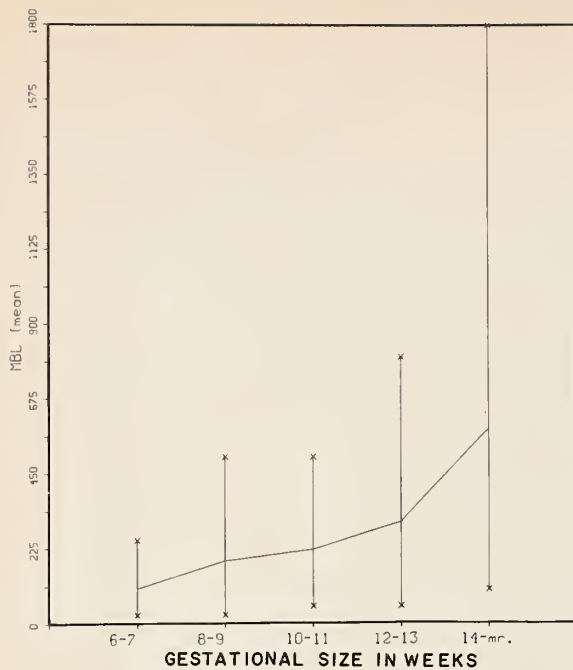


Chart 4.—Measured blood loss (MBL) related to length of gestation at time of abortion.

the average loss was approximately 200 ml, when estimated by the operating surgeon. At 12 to 13 weeks, this value rose to 280 ml, and at 14 weeks to just over 300 ml. By way of comparison, when measured fluid loss was studied (Chart 4) and related to gestational size, the means are as follows: six to seven weeks, 110 ml; eight to nine weeks, 180 ml; 10 to 11 weeks, 200 ml; 12 to 13 weeks, 300 ml; and 14 weeks, 560 ml.

Complications of Therapeutic Abortion

Table 1 shows operative and postoperative problems that occurred with each type of procedure.

Complications and Patient Age. Compared with the entire population at risk, there is no distinct age group with an increased operative risk. However, when postoperative complications are related to age, it was found that there was significant increased risk of postoperative problems in patients 30 years old and over. This group accounted for only 14.7 percent of the population, yet had 27.0 percent of all postoperative problems.

Complications and Duration of Gestation. Chart 5 relates operative problems to uterine size at the time of abortion. When compared with the total group, it is evident that interfer-

TABLE 1.—Complications of Therapeutic Abortions

Dilatation and Curettage for Therapeutic Abortion (431 Cases)	
A. Operative Complications	Percent of All D&C's Done
Hemorrhage at surgery requiring transfusion	1.2
Tenaculum laceration of cervix requiring suture	2.3
Cervical laceration with Vibrodilator	0.2
Uterine perforation	1.2
Dilatation failure—Hysterotomy performed	0.2
Dilatation failure—later successful	0.2
Failure to evacuate products of conception	0.2
<i>All Operative Complications</i>	<i>5.5</i>
B. Postoperative Complications	
Temperature of 100.4°F or greater with no other positive findings	2.0
Endometritis	0.9
Peritonitis requiring laparotomy and further surgery	0.9
Repeat D & C for retained products of conception	0.9
Urinary tract infection (proven by culture)	0.3
Endometritis plus retained products of conception	0.5
<i>All Postoperative Complications</i>	<i>5.5</i>
<i>Total Operative and Postoperative Complication Rate = 11.0%</i>	
Hypertonic Saline Solution Injection for Therapeutic Abortion (104 Cases)	
A. Operative Complications	Percent of All Injections Done
Saline failure—D & C done for abortion	6.7
Saline failure—Hysterotomy or hysterectomy done for abortion	13.4
Saline failure—Transvaginal saline injected	1.9
<i>Total Operative Problems</i>	<i>22.0</i>
B. Postoperative Complications	
Temperature of 100.4°F or greater with no other positive findings	3.8
Endometritis	0.9
Retained products of conception necessitating dilatation and curettage	8.6
Urinary tract infection (proven by culture)	2.8
Manual removal placenta with spinal anesthesia	0.9
<i>Total Postoperative Complications</i>	<i>17.0</i>
<i>Total Operative and Postoperative Complication Rate = 39.0%</i>	
Complications of Primary Hysterotomy-Hysterectomy vs. Hysterotomy-Hysterectomy Done after Saline Solution Failure	
Primary Hysterotomy-Hysterectomy (32 Cases)	Secondary Hysterotomy-Hysterectomy (14 Cases)
OPERATIVE:	
(Percent)	(Percent)
6.2	7.1
Hemorrhage at surgery requiring transfusion	
POSTOPERATIVE:	
43.5	36.0
Temperature of 100.4° or greater with no other positive findings	
0.0	14.3
Endometritis post hysterectomy	
0.0	7.1
Urinary tract infection	
49.7	64.5
Total Operative and Postoperative Complications	

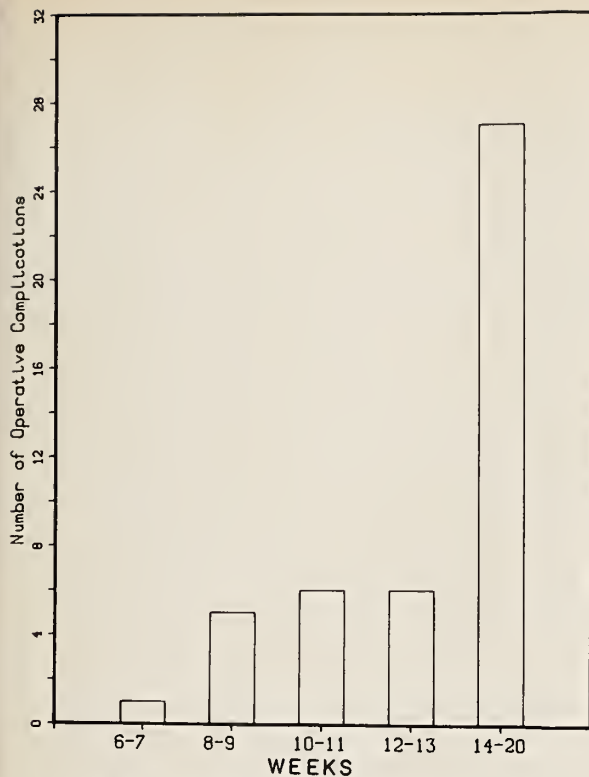


Chart 5.—Relation of operative complications to duration of gestation at time of abortion.

ence in gestations between six and 13 weeks results in a relatively low risk, but interference between 14 and 20 weeks, although accounting for 25.7 percent of procedures entailed 64 percent of all operative complications. When postoperative problems were evaluated with regard to uterine size, a similar complication rate occurred: patients who had abortion between 14 and 20 weeks had 62 percent of all postoperative problems.

Complications and Number of Pregnancies. The primigravidas had a relatively low risk. They were 57.8 percent of the study group, had 29 percent of the postoperative problems. Gravidas 4 or more had a significantly increased risk—16.8 percent of the study group, 47 percent of the complications.

Follow-up

Table 2 contains a detailed tabulation of the follow-up data received on 473 patients (83.3 percent) of the total population. Of interest is that of the 567 patients who had abortions there were only two known repeaters, both of whom had a second abortion at our hospital.

Comment

The increase in therapeutic abortions since the inception of the new California law in November 1967 can be attributed to referrals from various services such as clergy counseling, crisis centers and abortion counseling services within the San Diego area. These groups have referred patients to local sympathetic physicians rather than to out-of-state or out-of-country facilities as they might have done before. The increased number of abortions between August and September 1969 was attributed to the availability of Medical funding, with the resultant increase in private patient referrals. Social workers were employed to guide the needy patient through welfare, and cost was no longer an obstacle. At present, 89 percent of the total case study population is under private physician care as compared with 61 percent at the beginning of this study. The availability of funding was reflected by the increase in numbers of single persons seeking a legal abortion. Contrary to popular belief, even before the legalization of abortion it was mostly single women who sought termination of pregnancy. In our study, 70 percent of the entire series were between 15 and 24 years of age. In the final six months of the study this group has represented 74 percent. Psychiatric consideration was the indication for therapeutic abortion in 97 percent of this group. This finding is consistent with previous studies throughout California.⁴

Counseling and guidance services did not reach all segments of the population, as is evident by the fact that proportionally about twice as many Caucasians as Negroes and four times as many Caucasians as Mexican-Americans had abortions. The Mexican-American tolerates the social encumbrances of pregnancy out of wedlock more readily than do either black or white Americans. Mexican-Americans are more restricted by their religious beliefs and are not ostracized from the family unit, the care of the child being placed often in the hands of the grandparents. With them, therefore, abortion is more a social than a medicolegal problem. This study demonstrates the fact that as affluence increases so do the social restrictions and that forced morality might breed subjective immorality and guilt.

Although complications are of high incidence, they are generally innocuous in type. Neverthe-

TABLE 2.—Follow-up Data on Patients after Therapeutic Abortion: San Diego Study*A. Total Follow-Up of Patients*

Total Number of Patients Aborted=567

Number of Patients with Reported Follow-Up=473 (83% of all cases)

Patients with No Problem on Follow-Up=392 (83% of all followed patients)

Patients Who Failed Return Appointment=49 (10.4%)

Patients with Problem at Follow-Up=32 (6.6%)

B. Follow-Up on Dilatation and Curettage

Total Number of Patients Aborted by D & C=431

Number of Patients with Follow-Up=356 (82.6% of all D & C cases)

Patients with No Problem=299 (84.0% of all followed patients)

Patients Who Failed Return Appointment=36 (9.8%)

Patients with Problem at Follow-Up=21 (6.2%)

Marked Depression—7 patients

Excess Bleeding—4 patients

Anemia—2 patients

Endometritis—5 patients

Parametritis—1 patient

Severe Cramps—1 patient

Urinary Tract Infection—1 patient

C. Follow-Up After Saline Injection for Abortion

Total Number of Patients Injected=104

Number of Patients with Follow-Up=91 (87.5% of all Saline cases)

Patients with No Problem=71 (78.0% of all followed patients)

Patients Who Failed Return Appointment=10 (11.0%)

Patients with Problem at Follow-Up=10 (11.0%)

Marked Depression—4 patients

Excess Bleeding—5 patients

Endometritis—1 patient

D. Follow-Up After Hysterotomy or Hysterectomy for Abortion

Total Number of Patients Aborted by Hysterotomy/Hysterectomy=32

Number of Patients with Follow-Up=26 (81.0% of all H/H cases)

Patients with No Problem=22 (84.0% of all followed patients)

Patients Who Failed Return Appointment=3 (12.0%)

Patients with Problem at Follow-Up=1 (4.0%)

Depression—1 patient

less, this study should serve to warn that physician who feels that storefront abortion clinics are without hazard. An analysis of these complications suggests that problems are directly related to the uterine size at the time of physical examination. The larger uterus, in turn, reflects delay in obtaining therapeutic abortion. Sixty percent of the operative and 63 percent of the postoperative complications occurred in pregnancies terminated after 14 weeks.

Evaluation of the postoperative complications associated with saline solution induction points to retained products of conception, with associated bleeding, as the major cause. In our follow-up study, five patients were readmitted to the hospital for dilatation and curettage because of bleeding after saline solution evacuation. The incidence of complications secondary to saline solution evacuation could be significantly decreased by routinely performing a postabortal curettage in all intra-amniotic inductions. The

high morbidity associated with hysterotomy or hysterectomy could also be lowered by establishing adequate drainage at the time of operation.

Delay in admittance to hospital was attributed to: (1) the denial of pregnancy, especially by young patients of low parity; (2) misinformation concerning the availability of abortion; and (3) difficulty in obtaining funding without family involvement. Patients who had private funding or previous existing Medi-Cal support were admitted to the hospital in the early first trimester. Factors that were impossible to evaluate statistically as a source of delay were: (1) obtaining an appointment with an emphatic gynecologist; (2) a delay in obtaining a letter from two psychiatrists in the first 18 months of the study and one psychiatrist in the last six months; (3) awaiting the weekly meeting of the Therapeutic Abortion Board; and, finally (4) delay in obtaining beds and operating room time. Delay in abortion is not only directly related to an in-

creased complication rate later, but also to increased duration of hospitalization with resultant increased cost.

The value of performing abortion early also points to the hazard of individual state residency requirements which cause a delay in admittance to hospital. Forcing a patient to wait a three-month requirement places her in a higher risk category, and she may even attempt to seek an illegal abortion. This may account for the fact that the legalization of therapeutic abortions did not significantly decrease the number of patients admitted to The Johns Hopkins Hospital because of complications of illegal abortion.⁴ Although there is no stated residency requirement in Maryland, the physicians attempt to limit the termination of pregnancy to residents of the state.

In order to protect resident teaching facilities, private patients should have the attending physician's history, physical, consent to operate form, and orders written before admission. Abortions may best be managed during the week-ends, when bed availability is at a maximum. Suction curettage could also be performed in separate outpatient operating and recovery room suites. If the pregnancy is beyond 12 weeks, hospital inpatient management is mandatory.

The maximum psychological effects of the situation are usually felt before admission and at the time of discharge. Patients who have dilatation and curettage under anesthesia can fantasize that the pregnancy never existed; not so the woman who labors and then delivers the product of conception in bed. It is quite evident to an observer that the patient undergoing abortion by labor induction is under a greater mental stress both before and after the delivery. When hysterotomy or hysterectomy is performed as a primary mode of terminating pregnancy, the patient has a scar to remind her of the occasion and upon which she can focus her guilt at various times throughout her life. It is for this reason that in-hospital social work referrals would benefit patients in need of guidance and would help reduce the guilt of those who equate the word abortion with illegality and sin. If the patient is ambivalent about terminating the pregnancy, or wishes to obtain future assistance for her anxiety state, psychiatric consultation is a necessity. It allows the patient to see the usefulness

of the social-psychiatric supporting team rather than be forced to seek a psychiatric consultation to obtain an end—that is, abortion. It allows for a closer psychiatric evaluation and support for the patient and, more importantly, allows the psychiatrist to function in his chosen role as a consultant.

The patient tolerates well the environment of a pregnancy termination ward, even using it as a form of group psychotherapy. Therefore, workshop programs should be established to educate hospital employees to the problems and psychodynamics of patients undergoing therapeutic abortion. Patients who are reticent about involving themselves in groups should be placed in other positions. Follow-up teams should also be available to desensitize the patient before she is discharged and to stress the necessity for contraceptive measures. Programs must also be devised for "fetal fathers" who feel an equal need for guidance during this period of stress. Group therapy programs are currently being established at University Hospital and Crisis Clinics within San Diego.

Paramedical personnel alone cannot manage all the medical problems associated with therapeutic abortion. The patient must be treated in her entirety, and this encompasses a multitude of medical disciplines. We are now entering a gray zone of social change when abortion is no longer considered a moral or immoral issue, legal or illegal; but we are dealing with a problem which demands new concepts which will enable the distraught girl or woman to cope with the mental encumbrances imposed by present-day culture. Pregnancy termination programs must be moral, ethical and efficacious or the medical profession will have failed to evaluate the pulse and demands of society.

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Therapeutic Abortions in California

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■ *Therapeutic abortions in California have increased from 5,030 in 1968 to 15,339 in 1969, and over 60,000 are estimated for 1970. Also, there are pronounced regional differences in therapeutic abortions relative to live births. In 1969 the San Francisco Bay Area had six times as many abortions (115 per 1000 births) as did the Los Angeles Metropolitan Area (19). Preliminary figures for 1970 indicate this difference may be narrowed to a two-fold difference by the end of the year.*

Experience in other countries indicates morbidity and mortality risks are high in procedures done after the twelfth week, and in California one abortion in four is done after this period.

Planning is needed to assure access to abortion services in all areas of the State and to meet the obligations of law and equity implicit in the Therapeutic Abortion Act. This should include counseling, follow-up, and referral services and not just the abortion procedure alone. Extension and more effective use of family planning services could substantially reduce unwanted pregnancies and the consequent demand for abortion. Efforts are also indicated to reduce the proportion of women terminating pregnancy after the twelfth week of gestation.

Deaths associated with illegal abortions have decreased from 35 in 1966-1967 to 22 in 1968-1969. This is consistent with the view that the number of illegal abortions is decreasing.

(NOTE: Data for 1970 recently became available. They are printed at the end of this article.)

THE CALIFORNIA THERAPEUTIC ABORTION ACT became effective 8 November 1967. It provides that abortions may be performed in hospitals accredited by the Joint Commission on Accreditation of Hospitals when a committee of the hospital's medical staff finds that there is a substantial risk that the continuance of the pregnancy would gravely

impair the physical or mental health of the mother, or if the pregnancy resulted from rape or incest. The law specifically prohibits therapeutic abortions after 20 weeks of gestation.

Along with the act, the California Assembly passed a resolution requesting the Department of Public Health to accumulate data on abortion practices and to present the findings in an annual report to the legislature. As a result of this resolution, a reporting system was established in

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TABLE 1.—*Age-Specific Percent Distribution and Ratios of Therapeutic Abortions to Live Births in California, November 1967-1969*

AGE	THERAPEUTIC ABORTIONS					
	Percent Distribution			Ratio Per 1,000 Live Births		
	1967 ^a	1968	1969	1967 ^b	1968	1969
Total, 10-49	100.0 (518)	100.0 (5,031)	100.0 (15,339)	9.2	14.8	43.5
10-14.....	5.8	3.6	2.2	c	c	c
15-19.....	23.2	25.5	29.9	12.3	22.2	78.2
20-24.....	23.4	27.1	31.8	5.7	10.6	36.6
25-29.....	16.4	17.2	15.7	6.1	9.8	25.2
30-34.....	14.7	11.6	10.1	10.9	14.4	37.0
35-39.....	10.2	10.0	7.0	16.0	27.7	60.7
40-44.....	5.8	4.3	2.7	31.4	42.6	88.6
45-49.....	0.6	0.5	0.3	c	c	c
Not Reported	—	0.2	0.1	c	c	c

^aNovember-December 1967.

^b1967 data adjusted to estimate ratio for complete year.

^cRatios not calculated for base less than 1,000.

Source: State of California, Department of Public Health, Bureau of Maternal and Child Health, Quarterly Reports of Therapeutic Abortions and Birth Records.

which each accredited hospital makes reports quarterly to the department. These reports are the basis for the data presented here. The material includes a description of the patient population, geographic and hospital variations in therapeutic abortion, an estimate of the potential induced abortions in the state and a brief review of deaths associated with abortion.

Basic Statistics

The abortion experience for the 26-month period November 1967-December 1969 is described in this report. During this time 22,646 applications were received from 279 hospitals; 20,888 of the applications (92 percent) were approved and the abortions performed. Nearly 92 percent of the applications indicated that continuance of the pregnancy would gravely impair the mental health of the mother. Slightly over 3 percent (647) of the applications were based on danger to the physical health of the mother, and the remaining 985 applications (5 percent) were because of rape or incest.

Although the experience analyzed at this time is relatively brief, some trends are evident. First, the number of applications has been increasing in each quarter of reporting. Second, both the proportion of applications approved and operations

performed have increased from 92 percent approved and 89 percent performed in 1968 to 97 percent and 94 percent, respectively, in 1969. There was also a shift in the reason for the application. In 1967, impairment of the mental health of the woman was given in 80 percent of the applications; by 1969, this reason accounted for over 93 percent of the applications.

Further trends are noted when abortions are related to live births (Table 1). In 1968, approximately 15 therapeutic abortions were performed for each 1,000 live births and in 1969 there were nearly 44 abortions per 1,000 live births. Preliminary figures for the first six months of 1970 show over 23,000 abortions with a projected total for the year of about 60,000. This indicates a ratio of 170 therapeutic abortions per 1,000 live births was reached in 1970.

Patient Characteristics

The descriptive information on the 20,888 women who had therapeutic abortions before January 1970 is presented in following paragraphs. Where applicable, the characteristics of women having abortions are compared with those of California women who had a live birth during 1967-1969.

Age and Race

The age distribution has shifted since the first months of the act with proportionately fewer older patients getting abortions (Table 1). Women 30 and over were 31 percent of the total in 1967, but were only 20 percent in 1969. Abortions in patients under 20 years of age constituted over 32 percent of the total in 1969, while only 17 percent of women who had a live birth were under 20.

There has been an increase in abortions for all age groups in relation to live births (Table 1). The highest ratios occurred in the youngest and oldest age groups; in 1969, for example, there were 78.2 therapeutic abortions per 1,000 live births in the 15-19 year age group and 88.6 in the group 40-44 years of age. This indicates that among pregnant women those at the extremes of maternal age are obtaining proportionately more therapeutic abortions.

The racial distribution of women having abortions compares closely with that of live births—87 percent white and 13 percent non-white.

Previous Pregnancies and Marital Status

Fifty-four percent of the abortions were performed on childless women while slightly less than 40 percent of the live births were to women in this category. There is also a large group of women, more than 20 percent, who sought abortion of a fourth or higher order pregnancy and this compares closely with the proportion in this category among the live births (19 percent).

Only 26 percent of the abortions were performed on women who were married. Half of the married women were in the fourth or higher pregnancy order while only 11 percent were in their first pregnancy. Fifty-seven percent of the women had never married and 86 percent of these were in their first pregnancy. Seventeen percent of the patients were of other or unknown marital status, and of these only 12 percent were in their first pregnancy.

Socioeconomic Group

Although no specific data about income or occupation are reported, an indicator of socioeconomic status is available from the expected source of payment for the procedure. Insurance and private payment are still reported most frequently as the expected source of payment—62 percent in 1969. The proportion covered by Medi-Cal (Title

XIX) has increased, rising from 6 percent in 1967 to over 22 percent in 1969.

It is estimated that about 50 percent of the births with hospital charges paid by Medi-Cal are out-of-wedlock. It is understandable that more such patients would seek abortions than pregnant women in general. Moreover, there are selective factors operating, as a single woman may become eligible for Medi-Cal by the circumstances arising from an out-of-wedlock pregnancy.

Gestation

The lapse between conception and abortion is of particular concern in patient management. After the 12th week of gestation, a saline solution injection procedure is often done. This usually requires a longer hospital stay, and produces increased demands on hospital staff. Moreover, higher rates of complication and mortality have been reported after the 12th week of gestation in countries where large numbers of legal abortions are done.¹⁻³

"Gestation" as used is estimated from a conception date two weeks after the reported last normal menstrual period. Based on this definition, 25 percent of therapeutic abortions are performed beyond the optimal gestation period. When weeks of gestation for various categories of abortion patients are reviewed, some differences are noted. The proportion aborted in the unfavorable gestational period increases to 30 percent for women 15 to 19 years of age, to 35 percent for Negro women, and to 38 percent for patients in county hospitals.

Because of the increased risks beyond 12 weeks, need for efforts to substantially reduce the proportion of abortions in the second trimester is indicated. Establishing community services for pregnancy testing and counseling for problem pregnancies could provide a setting for earlier diagnosis and effective referral, thereby lowering the proportion of late therapeutic abortion procedures.

Geographic and Hospital Variation

There are pronounced differences in abortion data between various geographic areas of the state (Table 2). The hospitals in the nine counties forming the San Francisco Bay Statistical Area account for 22 percent of the live births. However, they reported 60 percent of the therapeutic abortions.

TABLE 2.—*Number and Percent of Therapeutic Abortions and Ratio Per 1,000 Live Births by Statistical Area California, November 1967-1969*

STATISTICAL AREA	Number and Percent 1967-1969	THERAPEUTIC ABORTIONS			
		Ratio Per 1,000 Live Births			
		1967 ^a 1969	1967 ^a	1968	1969
California	20,888 (100.0)	22.8	9.2	14.8	43.5
North Coast	15 (0.1)	2.4	2.2	2.2	2.7
Sacramento Valley	1,373 (6.6)	31.0	7.9	17.8	66.5
Mountain	85 (0.4)	6.5	3.4	3.6	12.3
San Francisco Bay	12,568 (60.2)	62.1	26.5	42.7	115.4
Central Coast	337 (1.6)	15.6	4.7	7.8	33.8
San Joaquin Valley	429 (2.1)	5.3	1.8	3.3	10.9
Santa Barbara-Ventura	677 (3.2)	24.0	8.4	15.7	46.1
Los Angeles Metropolitan	4,060 (19.4)	10.2	4.5	6.5	19.1
San Diego Metropolitan	960 (4.6)	14.8	3.0	5.7	33.8
Southeast	384 (1.8)	6.7	1.8	4.5	13.3

^a1967 data adjusted to estimate ratio for complete year.

Source: State of California, Department of Public Health, Bureau of Maternal and Child Health, Quarterly Report of Therapeutic Abortions.

On the other hand, hospitals in the Los Angeles Metropolitan Area (Los Angeles and Orange Counties) with 44 percent of the live births, performed 19 percent of the abortions. Expressed as a ratio, for 1969 there were 115 abortions per 1,000 live births in the Bay Area and 19 per 1,000 in the Los Angeles area—six times as high in the former as in the latter.

Preliminary figures for the first half of 1970 indicate the difference between the Los Angeles and Bay Area is narrowing. Los Angeles reported 7,915 abortions and the Bay Area 9,241 in the first six months of 1970. This suggests that the ratio of abortions to live births in the Bay Area will be approximately twice that of Los Angeles in 1970.

Four areas have lower abortion ratios than Los Angeles (Table 2). These account for about 16 percent of the total births and are largely rural and agricultural communities. It is likely that a number of factors are involved in the relatively low ratios in these areas. One is that they are traditionally more conservative than the urban areas. Second, in small communities it is difficult for an abortion patient to remain anonymous. Third, some women in these areas probably go to urban centers for abortion.

Although a number of reasons can be suggested for the difference between Los Angeles and the San Francisco Bay Area, the probable explanation lies in the variation in response of individual hos-

pitals. The basis for this view is seen in the distribution of abortions by hospital. From November 1967 to the end of 1969, 279 hospitals reported one or more abortions. Of these, 235 hospitals accounting for 75 percent of the births reported 19 percent of the abortions. In this same period each of nine hospitals reported more than 500 abortions. These institutions, which had 8 percent of the live births, had nearly 40 percent of the total therapeutic abortions. Seven of these hospitals are in the San Francisco Bay Area and only one is in the Los Angeles Area. From this it is evident the distribution of therapeutic abortions does not follow that of newborn and obstetric care and that hospitals in general have not organized to serve the new group of patients seeking therapeutic abortions.

This raises two issues of concern to the medical community. First, the concentration of abortions in a few hospitals moves away from the concepts of family practice and a continuing patient-doctor relationship. Second, although the Therapeutic Abortion Act does not require that a physician perform abortions or that a hospital accept a patient for that purpose, it does provide that under certain conditions a woman has a right to have an abortion. How, then, are such women to secure their rights if hospitals or physicians do not provide therapeutic abortions in their communities?

To correct regional disparity in abortion services, it is advisable that interested physicians

and hospitals develop plans to assure that adequate services are available throughout the state. In this manner the medical community can meet its obligations to law and equity, and subsequent regional differences in legal abortion can be attributed to the attitude and practice of the patient population rather than to a failure to provide service. Such planning will necessarily view abortion beyond the logistics of providing the surgical procedure. Whether a hospital has a few or many abortions, effective counseling, follow-up and referral efforts are needed to assure that family planning and social services are known and accessible to the abortion patient. Short of this, repeated unwanted pregnancies and further abortions will frequently be the sequel to this surgical procedure.

Abortion Deaths

No therapeutic abortion deaths had been noted by the reporting hospitals through December 31, 1969. However, two such deaths were identified in the department's regular surveillance of maternal mortality based on death certificate review. This implies a mortality rate of 1 per 10,000 abortions, less than half the 1968 maternal mortality rate of 2.9 deaths per 10,000 live births. Oral contraceptive use is associated with about 0.3 thromboembolic deaths per 10,000 women per year.⁴ Thus, a year's use of "the pill" is considerably safer than either delivery or abortion.

There continue to be a number of abortion deaths resulting from illegal procedures. In 1966 and 1967 combined, there were 35 maternal deaths in which underlying cause of death was reported as criminal or self-induced abortion. In 1968 and 1969 the number of deaths due to illegal abortion fell to 22. This is consistent with the view that the reduction in abortion deaths is due to using therapeutic abortion rather than an illegal or self-induced abortion.

Estimates of Total Abortions and Future Trends

For accurate evaluation of the impact of the abortion law on childbearing experience of California women, therapeutic abortion figures should be related to the total number of pregnancies (conceptions) and to spontaneous and illegal abortions. Although the number of pregnant women who have illegal and spontaneous abortions in

California is not known, a recent survey of both spontaneous and illegal abortions in urban North Carolina⁵ provides a basis to estimate the number of illegal abortions in California. The survey estimated that the proportion of women in the 18-44 age group having induced abortion in a year was 13.9 per 1,000 white women and 68.1 per 1,000 non-white women.

Applying these rates to the number of women ages 15-44 in California during 1969, estimated total abortions would be about 84,000. Even assuming that each therapeutic abortion resulted in one less illegal abortion, there would have remained an estimated 69,000 illegal procedures in 1969. Based on this assumption the rate for all induced abortions in 1969 was 238 per 1,000 live births with legal abortions accounting for 18 percent of the total.

The potential upper limit for abortions in California can be projected by combining the number of induced abortions and the number of unwanted births. A recent estimate done by Bumpass et al⁶ shows the proportion of unwanted births in the United States to be at least 20 percent. This proportion applied to the 1969 California live birth figure of 353,005 gives an estimated 70,600 unwanted births.

If all the unwanted births had been terminated by abortion, the 1969 births would have decreased 20 percent to 282,400; while total abortions would have increased to 154,600 (84,000 induced abortions plus 70,600 unwanted pregnancies). This would result in a ratio of 547 therapeutic abortions to 1,000 live births. The ratio is well under Japan's 912 to 1,000 and Hungary's 1,356 to 1,000 but exceeds Czechoslovakia's 344 to 1,000.

This projection is probably in the high range because allowances have not been made for the proportion of women with unwanted pregnancies who find abortion unacceptable. Even so, it is likely that total therapeutic abortions in 1970 exceeded 60,000. This is four times the number performed in 1969 and as yet there is no indication that the rate of increase is leveling off. In these circumstances a twofold increase, to more than 100,000 therapeutic abortions, can be expected in 1971.

Another factor which could ultimately affect the abortion rate is extension of family planning services. Abortion, legal or illegal, and unwanted births can be reviewed as primary prevention fail-

ures in family planning. A problem of considerable magnitude is implicit in 84,000 abortions and some 70,000 unwanted births in a year. At this point California appears embarked on a course of secondary birth control by providing 100,000 to 150,000 abortions a year. These numbers suggest that much remains to be accomplished in providing adequate family planning services, which are safer and less expensive than abortion as a primary birth control method. Such services, accompanied by wide community support, educational efforts and the removal of legal and administrative barriers for serving minors can be effective in reducing the number of unwanted pregnancies and their costly consequences.

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Addendum: The abortion figures for 1970 now have been assembled. More than 62,000 cases were reported. The four-fold abortion increase in 1970 over 1969 did not materially change the age, race, gravidus and marital status distributions reported above. The only major shift has been that the proportion covered by Medi-Cal rose from 22 percent in 1969 to over 35 percent in 1970.

As predicted, the differences in abortion ratios between the Los Angeles Metropolitan Area and the San Francisco Bay Area narrowed in 1970. Los Angeles had approximately 167 abortions per 1000 live births; the San Francisco Area had 254, or 1.5 times that of Los Angeles.

Although there has been a pronounced increase in the number of therapeutic abortions in 1970, with 365 hospitals reporting one or more procedures, a small number of hospitals continued to do a large portion of the procedures. Seventeen hospitals reported more than 1000 abortions in 1970, accounting for over 40 percent of the total.

Six of these are in the Los Angeles Metropolitan Statistical Area and eight in the San Francisco Bay Statistical Area.

Three deaths were reported in association with therapeutic abortions in 1970. One was due to a medical condition which was the indication for the operation itself. The other two deaths were due to hemorrhage in one case and embolism in the other. Based on this information the therapeutic abortion mortality rate is approximately 0.5 per 10,000 procedures. Some reservations are needed as to the completeness of reporting deaths. It is possible that not all the deaths associated with therapeutic abortions in 1970 were noted in the reporting system. A review of 1970 death certificates is under way and this will provide a better basis for determining the mortality risk.

The decided rise in therapeutic abortions indicates an increasing demand for and use of this procedure as a means of dealing with an unwanted pregnancy. In spite of this, the 1969 California vital statistics show over 40,000 illegitimate births and projections indicate such births are increasing. The irony of increasing therapeutic abortions and rising illegitimacy point to the need for more effective educational and family planning programs.

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"THE PILL" CAN DRY UP CONTACTS

"Dry eyes from oral contraceptives is a . . . fairly frequent finding in refitting contact lenses in our office. If the patient decides to discontinue the medication, it is our clinical impression that adequate tears for wearing contact lenses may not return for a year. Some patients taking the pill develop symptoms of burning and photophobia (with relief from installation of artificial tears or any kind of drops) even when they're not wearing contact lenses. It might be well to remember that some unmarried teenage girls have been given the pill for treatment of dermatological problems or regulation of menses."

—PAUL R. HONAN, M.D., Indianapolis
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Multiphasic Health Testing in the Clinic Setting

JOSEPH LADOU, M.D., Palo Alto

■ *The economy of automated multiphasic health testing (AMHT) activities patterned after the high-volume Kaiser program can be realized in low-volume settings. AMHT units have been operated at daily volumes of 20 patients in three separate clinical environments. These programs have displayed economics entirely compatible with cost figures published by the established high-volume centers.*

This experience, plus the expanding capability of small, general purpose, digital computers (minicomputers) indicates that a group of six or more physicians generating 20 laboratory appraisals per day can economically justify a completely automated multiphasic health testing facility. This system would reside in the clinic or hospital where it is used and can be configured to do analyses such as electrocardiography and generate laboratory reports, and communicate with large computer systems in university medical centers. Experience indicates that the most effective means of implementing these benefits of automation is to make them directly available to the medical community with the physician playing the central role.

Economic justification of a dedicated computer through low-volume health testing then allows, as a side benefit, automation of administrative as well as other diagnostic activities—for example, patient billing, computer-aided diagnosis, and computer-aided therapeutics.

THE PRACTICE OF AUTOMATED multiphasic health testing (AMHT) is stereotyped in the minds of most physicians. The Kaiser-Permanente Oakland Center has become a model for almost all clinic and hospital screening facilities, designed to process by large computer systems the physiologic test data of at least sixty examinees per day. Many metropolitan areas have such facilities.

Benefit-cost analyses of AMHT projects have demonstrated that economy is clearly a function of system utilization.^{1,2} Hence, most product development and systems engineering is aimed at

the medical centers with high-volume patient flows. Recognizing the high costs of these systems, most small sized physician groups are discouraged from implementing an automated testing facility.

Multiphasic health testing generates large amounts of data on each patient. This dictates that some form of automated data processing is necessary. In large AMHT centers the data is normally handled as an off-line batch process since it is referred to physicians outside the center. In the low volume setting, however, the testing is done at the physician's office. The need exists for immediate reporting of test results in a format that presents the information clearly, accurately and concisely.

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The need to retain maximum cost saving in AMHT projects is being repeatedly emphasized. Dr. Morris Collen of the Kaiser-Permanente AMHT cautioned participants at the 1969 Deerfield Meetings that groups offering multiphasic health testing services priced above \$25 could not meet the market.³ Many insurance companies have demanded the same price constraints in view of the benefits accrued from the screening concept. Having agreed that the \$45 million spent annually on pre-insurance examinations is excessive, the Retail Credit Company and the American Service Bureau, representing over one hundred insurance companies, are beginning the operation of nationwide paramedical testing units which within three years will compete directly with the contribution of the practitioner in determining insurability for low policy limits.

The physician who wishes to utilize the concept of multiphasic health testing recognizes that this service is available in only the very large clinics and hospitals, or by referral to an ever-increasing number of government supported screening centers. The average practitioner cannot generally comment on the reliability of automated testing results outside of his practice. Whether or not he is impressed with the value of multiphasic testing, he is obliged to interpret data and initiate treatment based on results from screening activities to which he is peripheral. In addition, he is the person upon whom the ultimate responsibility rests for a patient's reactions to a normal health appraisal or a diagnosis of early disease.

This is not a criticism of multiphasic health testing. The concern is expressed only with the delivery of medical services that make the physician a remote member of the team and, in so doing, cause him to feel uncertain about the quality of these services.

In summary, then, the factors that limit the participation of most physicians in programs of multiphasic health testing are (1) the cost of a large computer system, (2) the relative lack of medical centers capable of supporting patient flows that realize the economy of the concept, and (3) the peripheral part most physicians play in mass screening of persons whose testing was not ordered by them.

Through a grant from the Office of Economic Opportunity, multiphasic health testing was carried out in a six-doctor clinic on a pilot basis.

Twenty patients per day were examined, using a two-room area, a nurse and a technologist. Medical histories were partially acquired by questionnaire. This was done in the common lobby area of the clinic. In the first AMHT room those tests not requiring disrobing or privacy were performed by a technician. These included audiometry, vision screening, spirometry and body measurements. The second room allowed complete privacy in which tests of blood pressure, electrocardiography, tonometry, ankle reflex and collection of blood specimens were performed. All these tests were done with standard test modules available in most clinical settings. The specific choice of test equipment and AMHT panel varies with different physician groups, but it results in closer supervision and greater confidence in test results when the physicians are in control of the operation of the AMHT unit.

In this intimate setting privacy was appreciated by the patients as much as was the freedom from herding associated with high-volume screening. The entire test panel was complete within one hour for most patients. Rapport was established between paramedical personnel and patients in this close association, and the physicians assumed a direct supervisory role in the operation of their unit. The two internists of the group participated most in supervision, although all the physicians visited the unit almost daily.

The physicians, skeptical at first, came to rely heavily on the reports generated. Physician time has not been studied per se, but each of the doctors reports significant savings in history-taking and written detail of the examination. The patients were recommended for the multiphasic health testing by their personal physicians in the clinic, and had a brief explanation of it in most instances. The most significant finding of this study was that a 94 percent follow-up rate was maintained in this setting, which was that of a borderline poverty population. As a result of the success of the pilot program, Area III Regional Medical Program has approved a grant for its continuation.

The problems encountered by institution of this low-volume AMHT unit were typical. They were primarily those of physician acceptance and patient utilization. In the clinic setting where the practitioner indicates to his patient that the AMHT panel will provide him with useful information, the problem of utilization of the system

TABLE 1.—Cost Analysis of a Low-Volume Automated Multiphasic Health Testing Facility Utilizing Existing Laboratory and X-Ray Departments in a Small Clinic.

<i>Fixed Costs (monthly)</i>			
<i>Overhead</i>		<i>Labor</i>	
Offices	\$ 400	Registered Nurse	\$ 700
Telephone	50	Technician	600
Office Equipment	80	Secretary (½ time)	275
Instruments	290		<u>\$1,575</u>
Insurance	20	10 percent Burden	159
System Lease (3 yrs.)	1,050	Physician Supervision (⅓ time)	260
System Maintenance	175	Total Labor	<u>\$1,994</u>
Contingency	170		
	<u>\$2,235</u>		
Total Labor	<u>1,994</u>		
Total Fixed Cost	<u>\$4,229</u>		
<i>Variable Costs (per examinee)</i>			
Disposables and Forms	\$ 1.00		
Data Handling	1.00		
Total	<u>\$ 2.00</u>		

is quickly overcome. The problem of physician acceptance is more complex. The tests performed in an AMHT unit are well known to practitioners, and their utilization of the testing system generally follows a brief period in which they gain confidence in the testing techniques and results and become acquainted with the format of the computer print-out.

Table 1 presents a cost analysis of a low-volume AMHT requiring a total of four rooms with a total space requirement of 500 square feet. The test panel is similar to that performed on each examinee in the above project. It is of interest to note that the traditionally labor-intensive activity of the high-volume AMHT is not evidenced by these costs. The fixed costs of a low-volume AMHT are largely those of overhead, reflecting better utilization of paramedical personnel to the minor disadvantage of equipment usage. These figures presume that the AMHT is free-standing and that labor and overhead costs are not distributed among other clinic activities. This is seldom the case in actual practice, which further lowers the operational costs of an AMHT system by drawing upon the paramedical personnel to perform other clinic functions, and to use the equipment for other purposes than multiphasic health testing.

Table 2 presents these costs as a function of daily patient flow through the AMHT. For example, with a patient flow of 20 per day, the cost per examinee would be \$14.50, to which would be added the cost of the laboratory panels for blood and urine tests and the cost of a chest x-ray

TABLE 2.—Per Patient Costs of Operating the Low-Volume Automated Multiphasic Health Testing Facility.

Examinees per Day ...	10	15	20	25
Examinees per Month .	170	255	340	425
Fixed Costs	\$4,229	\$4,229	\$4,229	\$4,229
Variable Costs	340	510	680	850
Total Costs	<u>\$4,569</u>	<u>\$4,739</u>	<u>\$4,909</u>	<u>\$5,079</u>
Cost per Examinee ...	<u>\$26.90</u>	<u>\$18.60</u>	<u>\$14.50</u>	<u>\$11.90</u>

film in the clinic where such a system is utilized. When indicated, the low-volume AMHT can be increased in patient flow capability by modular addition of pairs of testing rooms.

Further experience gained with an industrial medical clinic largely specializing in preventive medical examinations demonstrated the value of making the physician the center point of multiphasic health testing. Here, utilizing the economy and pragmatism of this concept, it has been shown that a two-doctor clinic specializing in industrial medicine can serve the needs of a 20,000 employee industrial area with ease and efficiency. The physicians rely heavily on paramedical personnel to perform pre-employment tests of vision, audiometry, spirometry, dynamometry and other standard parts of the multiphasic panel. Time savings in the practice of preventive medical examinations approximates 50 percent. The pre-employment candidates, though generally young, are found to have a greater than 10 percent incidence of significant illness, which is then reported to the personal physician. In virtually all

cases, the consumer of medical services is pleased to receive a more thorough evaluation, and the medical delivery system operates with greater economy and efficiency through use of the multiphasic health testing concept. Yet the most important ingredient in this success is the support of the physician who sends the patient through the testing panel and assumes the ultimate responsibility for the results at its completion.

After economic benefits and the simplicity of low-volume testing are demonstrated and physician and patient acceptance are obtained, the problem of automation must be addressed. The time-consuming problems of recording and reviewing a large mass of data make the need for automation clear. In the past three years the advent of the minicomputer has brought the problem to solvability. Small, general purpose digital computers that just two or three years ago cost \$15,000 now cost as little as \$5,000. In addition to decreasing costs, the capabilities of small computers are increasing rapidly with development of faster memories and miniaturization of circuits.

Minicomputers are being dedicated to numerous medical applications. Low cost makes them compatible with low-volume multiphasic health testing. For example, a small computer used to control the "branch-chain" medical history interview in a clinical setting can also process the reports of a number of audio-visual terminals. The computer is housed in the small cabinet, and can as well be placed in the secretarial area of the clinic where the report it generates will not be disruptive to the patient. It can also be configured to do analyses such as vector or scalar electrocardiography and data acquisition for laboratories; and an advantage over time-shared computers is that it resides with its owners. It offers complete confidentiality of medical records, and it saves the user from connect time charges for time-share computers, which are quite high for biomedical applications.

These cost considerations indicate that a group of six to ten physicians generating a need for 20 multiphasic health appraisals per day is able to economically justify the use of a computer located at the site of their practice. A typical low-volume AMHT utilizing a dedicated small computer would cost less than \$50,000 and lease for under \$2,000 a month to provide per patient costs consistent with Table 2.

With the computer justifying its presence in the private practice setting through use in low-volume health testing, a number of alternate activities become economic. Standard programs have been developed for administrative data processing. Patient billing is a common application of automation in medicine. It has been shown that computer billing for medical services increased more in the last three months of 1969 than in the previous two years.⁴ Management reports, inventory control and various other functions can be performed by the small computer with standardized instructions during the night hours when testing is not the primary activity of the system. Large computers are already being utilized to present, by a time-share mode, differential diagnoses for common disease complexes. General use of computer-aided diagnosis is premature, but recent operating programs have demonstrated its feasibility.⁵⁻¹¹ The natural follow-on to this is computer-programmed therapeutics. The infinite number of choices of drugs for an equally large number of disease conditions, with the confusing number of side-effects and contraindications, are natural activities of a computer system in the medical setting. The small computer can provide all these capabilities by acting as an intelligence terminal communicating with the large computer systems of the medical university complexes.

The small computer, with its natural advantages of immediate availability and low cost, has an increasing applicability to medical needs. The automation of multiphasic health testing units in group practices and small hospitals is but one.

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Cancer of the Pancreas in California, 1942-1967

The California Tumor Registry Experience

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■ *California Tumor Registry data on pancreatic cancer for the period 1942-1967 (6,344 cases) was reviewed. Ninety-five percent of the cases were diagnosed after age 45. A male to female sex ratio of 1.5:1 was noted. In the 6,344 cases there were no Chinese females.*

Relative survival rates in the period covered ran between 1.8 and 2.3 percent. The mean survival from time of diagnosis was only 2.2 months, far worse than reported elsewhere.

High incidence, low median age at diagnosis, and poor survival in Negroes suggest the need for a broader epidemiologic study focusing on specific predisposing factors in that race.

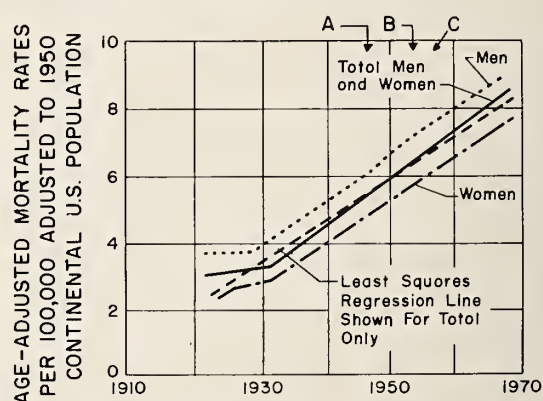
IN THE LAST TEN YEARS cancer of the pancreas has become the third leading cause of cancer death among males ages 35 to 54.¹

Since 1920 the age-adjusted incidence and mortality rates for pancreatic cancer have trebled (Chart 1). This article will detail the epidemiologic, treatment and survival experience for this disease from California Tumor Registry data for the 25 years of follow-up available (1942-1967).

Krain² recently reviewed the literature and summarized the environmental factors that have the best epidemiologic evidence to support a true linkage with pancreatic cancer—(1) cigarette smoking^{3,4,5} and (2) industrial chemical exposure.^{6,7}

Other factors—such as alcoholism, for example—require better controlled epidemiologic studies to determine their influence on the incidence

of pancreatic cancer. Krain also showed that the increase in pancreatic cancer is real and not due to statistical or classification artefacts.²



- A Fifth Revision of Manual of International Causes of Death 1948-1951
- B Sixth Revision of Above Manual 1954
- C Seventh Revision of 1957

Chart 1.—The rising mortality of pancreatic carcinoma in the United States 1920-1970 by sex using age-adjusted rates. Source: World Health Organization (1965) and American Cancer Society (1969).²

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TABLE 1.—Pancreatic Cancer Age-Adjusted Average Annual Incidence Rate by Race and Time Period, Alameda County, California, 1960-1967. (Excludes In Situ Cases)

Race	Years		
	1960-1962	1963-1965	1966-1967
Number of Cases			
All Races	228	269	191
White	207	224	171
Negro	17	41	17
Age-Adjusted Incidence Rate			
All Races	7.5	8.7	9.1
White	7.5	8.2	9.4
Negro	7.3	15.4	7.7

Note: Rates are per 100,000 population. Age-adjusted rates were computed by the direct method, using the 1950 population of the Continental United States as the standard.

Source: State of California, Department of Public Health, Alameda County Cancer Registry Records, 050070.

Newer diagnostic procedures such as arteriography, radioisotopic scanning and enzymatic tests have been developed for pancreatic cancer diagnosis. Better palliative and curative surgical procedures have been devised in the last ten years. Chemotherapy—with 5-fluoracil—has entered the treatment spectrum.

Therefore, pancreatic cancer was examined for data bearing on diagnostic and survival experience with the aim of providing the medical practitioner with a compendium of background information.

Materials and Methods

The California Tumor Registry is a cooperative undertaking of 58 California hospitals and the State of California Department of Public Health. By combining the experience of many hospitals, a larger and more representative series is obtained than could be expected from any single hospital. The Registry has collected data on more than 300,000 cancer cases, 20,000 new cases being added each year. Details on methods of study are elaborated in previous publications.^{8,9,10}

Data on incidence rates was based on material generated by the population based⁹ Alameda County Cancer Registry, a unit of the California Tumor Registry. Data on histologic confirmation, staging of the disease, mode of treatment and

TABLE 2.—Average Annual Pancreatic Cancer Incidence Rates by Race and Sex, Alameda County 1960-1964, Age-Adjusted (per 100,000 population)

Race	Males	Females	Total
Caucasians	9.6	6.4	7.8
Negroes	13.0	6.0	9.0
Chinese	11.11	—	6.2
Japanese	5.9	6.3	6.0
		7.9	Total (402 cases)
Japanese in Japan (1960-1964) Median 4.0 per 100,000 Population (based on 15 percent histological confirmation)			

survival were derived from the experience of the California Tumor Registry. To assure comparability, data used in this presentation were taken from 44 hospitals that were in the Tumor Registry for the entire time covered by this report—1942-1967. There were 6,344 cases, approximately 91 percent of them histologically confirmed.

Results and Discussion

Diagnostic Considerations

Trends. Table 1 shows the Alameda County incidence trend, which parallels that of the United States (Chart 1). The proportion of localized cases at the time of diagnosis has remained relatively unchanged (since 1942) at 13 percent.

Age At Diagnosis. Ninety-five percent of pancreatic cancer cases were diagnosed after age 45. The median ages at which diagnosis was made were, for Caucasians, 65.3 years; for Negroes, 54.1 years; Japanese, 62.1 years; American Indians, 56.1 years.

This data should be viewed with caution since there were only 11 cases in American Indians. Table 2 shows the high incidence of pancreatic cancer in Negroes. This coupled with the low median age of diagnosis (and hence age at death) emphasizes the magnitude of the toll of this disease in Negroes. It should be noted that persons of races other than Caucasians and Japanese may die mainly of other causes such as heart disease and automobile accidents and thus fewer older people of these races survive to be at risk of pancreatic cancer.

TABLE 3.—Pancreatic Cancer—Observed Survival Rate by Race (California Tumor Registry, 1958-1967)

Race	Number of Cases	Months after Diagnosis (Observed Rate—Percent)				
		1	2	3	4	5
All Races ¹	3,301	84.0	59.0	44.3	35.1	28.1
White	2,899	83.9	58.8	44.1	35.1	28.1
Negro	341	85.6	59.2	45.2	34.8	27.1
Japanese	29	86.2*	61.1*	46.7*	32.3*	28.7*

¹Excludes 16 cases of unknown race or age.

*Rate has a standard error between 5.0 percent and 9.9 percent.

Note: Rates are based on cases first diagnosed in 44 California hospitals. Observed rates are calculated by the actuarial method.

Source: State of California, Department of Public Health, California Tumor Registry Records, 050070.

Sex. The ratio of male to female in cancer incidence rates (for Alameda County Registry incidence data) for races having sufficient numbers to be statistically valid (1960-64) was 1.5:1, approximately the same ratio noted by Segi and Kurihara in analyzing data for 24 countries.¹¹ This ratio remains predominantly male between the ages of 35 and 54 for both Alameda County Tumor Registry and the non-population based California Tumor Registry data as a whole, indicating that the California Tumor Registry is somewhat representative of the population in California.

Race. Pancreatic cancer (I.C.D. No. 157) occurs in all races in the California Tumor Registry material. The absence of pancreatic cancer in Chinese females (Table 2) for the California Tumor Registry as a whole deserves further study.

Survival Considerations

Trends. Since 1942, the five-year relative survival rate for both sexes has increased only slightly, from 1.8 to 2.3 percent (cumulative case total for all stages). For cases localized at the time of diagnosis the five-year relative survival rate for this period has ranged from 5.2 to 7.4 percent. Table 3 shows the survival experience that was observed in the last ten years when, theoretically, better treatment measures were available. The mean survival of 2.2 months from time of diagnosis is even worse than that noted in a recent Connecticut study (4.3 months).¹² Thus, it is unfortunate that mortality data still approximates the incidence data for this disease,

TABLE 4.—Standardized Relative Frequency, Male and Female, Pancreatic Cancer Cases by Site and Type of Hospital, 1942-1956

	Number of Cases				Standardized Relative Frequency	
	County		Private		County	Private
	Observed	Expected	Observed	Expected		
Males	784	666	849	967	118	88
Females	464	367	648	745	127	87

Source: California Tumor Registry.

for which diagnostic accuracy still remains only 30 to 33 percent.¹³

Age and Sex. There was no significant difference by age or sex for pancreatic cancer survival from California Tumor Registry data ($p>10$), for the period 1942-1967.

Race and Socioeconomic Class. Table 4 shows that cancer of the pancreas was more common in county hospitals than in private hospitals. This inverse relationship between pancreatic cancer and socioeconomic class was also noted by Dorn and Cutler.¹⁴ Negroes, with their higher incidence of pancreatic cancer and higher admission percentage to county versus private hospitals in California, thus deserve attention in terms of future epidemiologic studies. This increasing incidence in Negroes (in whom the disease is diagnosed at lower median ages than in Caucasians—at a working age in fact) suggests that attention be given to occupational health studies in Negroes ages 35 to 54. Differences between Caucasians and Negroes in susceptibility to industrial chemicals or cigarette smoke may well explain the difference in incidence of pancreatic cancer.

Treatment. Only 5.5 percent of patients were treated surgically (for palliation); 92.4 percent had no treatment or only supportive treatment, while combination treatments and cases in which the treatment was not known made up the remainder. Less than 2 percent of cases received chemotherapy, indicating that chemotherapy is still largely confined to a few cases at large teaching hospitals or that such treatment was lumped with supportive treatment in initial hospital coding.

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Phenylketonuria and Its Variations

A Review of Recent Developments

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SENSITIVE METHODS FOR SCREENING newborn infants for elevation of blood phenylalanine have been widely used in the past six years. This screening has caused a revolution in concepts about phenylketonuria (PKU). The discovery of hyperphenylalaninemic conditions which to a variable degree biochemically can mimic true PKU has demanded increasing knowledge of the pathophysiologic features of PKU and has necessitated changing methods of diagnosis and management. An enormous expenditure in research time and effort has produced much data, not all of it significant. This article is intended to review some of these facts and concept changes and to put them in historical context.

Historical

The concept of PKU was static until screening programs based on the method of Guthrie and Susi¹ for detection of elevated serum phenylalanine levels came into use. As recently as the early 1960's, it was generally believed that any prolonged elevation in serum phenylalanine level

(hyperphenylalaninemia) invariably led to mental retardation. Historically, this belief was not unreasonable, but it reflected the bias that results when screening programs focus on special or selected populations. The clinical and biochemical features of PKU were first defined in severely retarded children.²

The first biochemical aberration found in these children was the urinary excretion of phenylpyruvic acid (PPyA).² This substance caused their urine to turn green when a 10 percent ferric chloride solution was added. When Fölling² screened the urine of institutionalized retarded patients with ferric chloride, he found other subjects with similar biochemical patterns and clinical courses. Fölling demonstrated that these patients had greatly elevated serum phenylalanine levels and defects in phenylalanine metabolism. His findings were later substantiated by Jervis,³ whose studies suggested greatly reduced activity of the hydroxylation enzyme which converts phenylalanine to tyrosine. An elevated serum phenylalanine level, urinary excretion of phenylalanine metabolites, especially PPyA, and retardation became synonymous with PKU in the minds of most clinicians.

Armstrong et al⁴ showed that often a considerable time after birth had to pass before PPyA could be detected in the urine of newborn PKU patients, and that its detection was unlikely if the

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method than the ferric chloride test. The Guthrie bacterial inhibition assay¹³ accomplished this by measuring serum phenylalanine directly.

Shortly after the inception of blood screening programs, it became evident that there was a need to re-define the criteria for diagnosis of PKU. This was because of the method of screening and the age and population sampled. Most patients identified by ferric chloride testing before the Guthrie method of screening was used were older and retarded. In contrast, Guthrie screening focused on clinically normal newborns. An unexpected consequence of the screening programs was that many more infants were identified with elevated serum phenylalanine levels than would have been predicted on the basis of previous statistical data from retarded populations. It was difficult to reconcile these differences at the time. With further screening it was evident that some hyperphenylalaninemic infants and children without concomitant retardation (variants) accounted for a portion of the discrepencies.¹⁴ A minor upheaval in the concepts about PKU was caused by the discovery of relatively large numbers of these variants. A similar sequence of events has occurred with other amino acid disorders. Biochemical abnormalities in homocystinuria, cystathioninuria and histidinemia were first detected in patients who were retarded or appeared retarded; but more extensive screening revealed that persons with obviously normal intelligence possessed the same biochemical aberrations.^{15,16,17} With time, increasing numbers of hyperphenylalaninemic but clinically normal infants and children are being recognized who have intermittently positive ferric chloride tests and variably increased excretions of the "characteristic" urinary metabolites of PKU; PPA and ortho-hydroxyphenylacetic acid (o-HPPAA). These variant patients, who at times biochemically simulate PKU patients, are an enigma and the cause of great confusion. Variants have made the definition of PKU arbitrary to clinicians and other investigators. Guidelines for the treatment of hyperphenylalaninemia are now based upon diagnostic criteria for PKU which are reasonably reliable although not absolute. (See section on treatment and Table 1.) At present patients with persistently elevated serum phenylalanine levels (hyperphenylalaninemia) can be divided into two groups: PKU and variants. We define as phenylketonuria, patients with serum phenylalanine levels persistently greater than 25 mg per 100 ml and with the ex-

pected urinary metabolites of PKU while ingesting an ordinary diet. All other patients with abnormal elevations of blood phenylalanine but without elevated blood tyrosine are classified as variants.

Screening

Following development of the Guthrie test, screening of newborn infants on a large scale spread throughout this country, Europe and other areas of the world. Laws requiring screening were enacted in the mid 1960's in most states in the United States, and in most states not having mandatory screening, widespread voluntary screening programs were organized.

The incidence of PKU in 1963, based on data from retarded populations, was estimated by Knox¹⁸ to be between 1:20,000 and 1:25,000 among patients from mixed European populations. Results of mass screening of newborns in Massachusetts between 1959 and 1963 by the Guthrie method suggested that the incidence of PKU was 1:7933.¹⁹ The incidence of hyperphenylalaninemia from the same center based on later newborn screening data was approximately 1:10,000 live births.²⁰ The incidence figures did not include patients with hyperphenylalaninemia associated with transient tyrosinemia, which has been shown to be the most frequent cause of transient mild elevations in serum phenylalanine.²¹

The incidence figures for PKU reported by screening and treatment centers, which were high shortly after initiation of the newborn blood screening programs, now are decreasing and approaching the figures calculated from the screening of retarded populations. The incidence of persistent hyperphenylalaninemia without tyrosinemia, which includes PKU and the variant disorders, has remained relatively constant in the United States at about 1:13,000 live births.²² The incidence of the variant disorder was estimated by Berman et al²² in 1969 to be 1:50,000. Hanley et al²³ showed the incidence of variants in Canada was 1:54,000. Subsequently, Hanley²⁴ suggested that the ratio between variants and true PKU is 1:2. A more recent report from Australia, however, suggests that the ratio is 1:1.²⁵

It is difficult to make comparisons of the incidence figures in the United States with figures from other countries. Reports have not always been specific about the diagnostic criteria for PKU. The conditions described may be different and comparisons of frequencies, therefore, may not al-

TABLE 1.—*Course of Untreated Phenylketonuria*

<i>Clinical</i>	<i>Laboratory</i>
Birth	
Physical: Normal	Serum: \pm elevated serum phe. normal serum tyr.
Neurological: Normal	Urine: \pm elevated phe metabolites
Development: Normal	EEG: normal
15 days to 3 months	
Physical: Eczema may be present, musty or vinegary odor of PAC	Serum: Phe. >25 mg %
Neurological: normal to variable increased irritability or lethargy, seizures \pm	Tyr. — normal or decreased
Development: normal to questionable delay in motor milestones	Urine: elevated phe, PPYA, <i>o</i> -HPAA + FeCl ₃ , +DNPH
	EEG: may be abnormal, i.e.: hypsarrhythmia, petit mal variant, multifocal spiking
3 months to 6 months	
Physical: Eczema may be present, odor present, 30 percent microcephaly	Serum: Phe. 30-100 mg %
Neurological: 50 percent with seizures, increased irritability or lethargy	Tyr. normal or decreased
Development: delays usually present and becoming more obvious	Urine: elevated phe, PPYA, <i>o</i> -HPAA + FeCl ₃ , +DNPH
	EEG: 90-95 percent with abnormal pattern, hypsarrhythmia, petit mal variant, multifocal spiking
6 months to 1 year	
Physical: Eczema frequently present, odor present, 30 percent mild microcephaly	Serum: Phe. 30-100 mg %
Neurological: 50 percent with seizures, increased irritability, rarely apathy and lethargy	Tyr. normal or decreased
Development: obviously delayed motor milestones	Urine: elevated phe, PPYA, <i>o</i> -HPAA + FeCl ₃ , +DNPH
	EEG: 90-95 percent with abnormal pattern, hypsarrhythmia, petit mal variant, slow waves, multifocal spiking
1 year to 3 years	
Physical: Eczema may be present, odor present, skin, hair and iris may be lighter than family, 30 percent mild to moderate microcephaly	Serum: Phe. 30-50 mg %
Neurological: 30-50 percent with seizures, increased tremors and irritability	Tyr. normal or decreased
Development: moderate to severe M.R., may have destructive and autistic behavior	Urine: elevated phe, PPYA, <i>o</i> -HPAA + FeCl ₃ , +DNPH
	EEG: 90 percent moderately to severely abnormal hypsarrhythmia, petit mal variant, slow waves, multifocal spiking
3 years to 6 years	
Physical: Eczema uncommon, odor present, skin, hair and iris lighter than family, 30 percent mild to moderate microcephaly	Serum: Phe. usually >20 mg %
Neurological: 30-50 percent with seizures, increased tremors, irritability	Tyr. normal
Development: moderate to severe M.R., may have destructive and autistic behavior	Urine: elevated phe, PPYA, <i>o</i> -HPAA + FeCl ₃ , +DNPH
	EEG: 30-50 percent abnormal, petit mal variant, slow waves, multifocal spiking
6 years to adult	
Physical: Eczema uncommon, odor present, skin, hair and iris lighter than family, 30 percent mild to moderate microcephaly	Serum: Phe. usually >20 mg %
Neurological: 10-20 percent with seizures, increased tremors, irritability	Tyr. normal
Development: moderate to severe M.R. may have destructive and autistic behavior	Urine: elevated phe, PPYA, <i>o</i> -HPAA + FeCl ₃ , +DNPH
	EEG: 10-20 percent abnormal, petit mal variant, multifocal spiking

Phe. = phenylalanine, Tyr. = tyrosine, PPYA = phenylpyruvic acid, *o*-HPAA = orthohydroxyphenylacetic acid, PAC = phenylacetic acid, FeCl₃ = Ferric chloride, M.R. = mental retardation.

ways be valid. Incidence figures reported and geographic variations are indicated in Table 2.

When centers reporting incidence figures are unable to make a firm diagnosis of a variant disorder, natural inclination would be to diagnose PKU, and to treat, because of the poor prognosis in untreated PKU. Patients with serum phenylalanine levels of 10 to 15 mg per 100 ml were reported

as having PKU, even without the presence of urinary metabolites characteristic of PKU. Many of these non-PKU patients were treated with restricted phenylalanine diets, and as a result diet-deficiency syndromes and even deaths were reported.¹² Screening programs have been criticized because of this.¹³

The consequences of misdiagnosis cannot be

TABLE 2.—Incidence Rates of PKU

Place	Reference	Method	Period	Number Tested	Cases of PKU*	Approximate Incidence
Massachusetts	26	Guthrie	1962-1964	217,752	27	1:8,000
Georgia	27	Guthrie	1/67-6/68	57,494	2	1:29,000
North Carolina	28	Fluorometric	1966-1967	151,734	6	1:25,000
Elkland County, Indiana.....	29	Phenistix with mail return	1961-1967	13,169	4	1:3,300
New York State.....	30	Guthrie	1965-1968	958,346	77	1:12,000
California	31, 32 33, 34	Various newborn blood	1966-1968	620,000	39	1:16,000
Oregon	35	Urine Guthrie	1963-1965 1965-1966	30,000	3	1:10,000
Ontario, Canada	23	Guthrie	1965-1968	392,098	26 (+ 5 Variants)	1:15,000 (1:13,000 including variants)
Israel	36	Guthrie	—	27,000	3	1:9,000
	37	Guthrie	—	178,174	7 PKU (+ 9 Variants)	1:25,000 (1:11,000 including variants)
Denmark	38	Phenistix by home visit or physician at approximately 5 weeks	4/67-10/68	320,000	15 (8 diagnosed after 5 weeks—4 were false negatives at 5 weeks)	1:21,000
		Guthrie	9/64-10/68	60,400	4 PKU (+ 2 Variants)	1:15,000 (1:10,000 including variants)
Ireland	39	Guthrie	2/66-5/67	62,856	14	1:4,500
France	40	Guthrie	—	79,730	9	1:9,000
Belgium	41	Guthrie	1965-1967	22,471	6	1:3,700

*Criteria for diagnosis not necessarily consistent between reports. Some reports of PKU are surely variants. See text.

minimized. In our opinion, however, the positive aspects have justified the screening programs. Screening programs have forced unproven concepts to be re-evaluated and some to be rejected. Increasing numbers of children and some adults who are clinically normal but biochemically abnormal have now been identified. Some infants who do not need dietary restriction have been found, and treatment has been stopped. Another important direct and beneficial consequence of the PKU screening programs has been the very early detection of infants with PKU. The average age of PKU patients at the time of detection has fallen dramatically from eight years to less than six months in one large treatment center.⁴⁴ It is

commonly believed that the prognosis for intellectual development is best when dietary treatment is started very early in infancy.⁴⁵

From the Collaborative Study for the treatment of PKU, based at Children's Hospital of Los Angeles, have come recent reports of a 2:1 ratio of males to females in the first 90 PKU infants identified by newborn screening.^{46,47} In an early report by Jervis¹⁸ of 50 cases of phenylketonuria a ratio of three females to two males was found. This seeming discrepancy has raised the question of whether female PKU infants are being missed by the present blood phenylalanine screening of newborns within the first three days of life. It is possible that a metabolic difference between infant males and

females accounts for a slower neonatal rise in blood phenylalanine levels in the female. The discrepancy may be an artifact of small sample size. Other possible explanations for a discrepancy have been suggested and further study is needed.⁴⁹ At present, we recommend that especially for females the PKU blood specimens be taken at the latest possible time before discharge from the newborn nursery. A urine specimen should also be checked with a Phenistix® at the first well baby visit. If developmental delay in any child is observed, a serum phenylalanine determination may be warranted regardless of whether or not phenylalanine was determined previously or what the results.

Variant Disorders

The unexpected finding of relatively large numbers of hyperphenylalaninemic children who are not retarded (variants) has spurred investigators to find a method for distinguishing them from children with PKU. Early studies to identify these variants were based on their ability to excrete or metabolize a standard "load" (amount) of phenylalanine. A four-hour oral tolerance test with L-phenylalanine 100 mg per kg of body weight had been used previously by Hsia et al⁵⁰ in genetic studies of parents of PKU patients to determine the heterozygous or carrier state. The disappearance rate of blood phenylalanine following the administration of L-phenylalanine was determined. This four-hour test did not differentiate the variant forms of hyperphenylalaninemia from PKU.²² However, extending the monitoring period to over 24 hours led to the recognition of at least two distinct patient populations.⁵¹ When phenylalanine was administered in the form of a balanced protein supplement such as whole or evaporated milk, findings were similar.⁵² Although most patients could readily be separated into two groups, PKU and variant, a few patients could not immediately be classified solely on the basis of loading studies. There appears to be a spectrum within the group of variant disorders.

Reports indirectly support the concept of at least two hyperphenylalaninemic patient populations; however, the evidence is scanty. Shortly after the Massachusetts mass screening of newborns was started, Kennedy⁵³ reported a series of atypical hyperphenylalaninemic patients whose blood phenylalanine levels were moderately high, but who were mentally normal or only mildly re-

tarded, despite lack of dietary restriction. The ethnic background of this group of patients was largely Italian, in contrast to the northern European background most frequently associated with PKU. Rosenblatt and Scriver⁵⁴ reported hyperphenylalaninemia in clinically normal patients of Mediterranean ancestry, and suggested that they represented a genetically distinct disorder from PKU. Another observation which may be pertinent is that PKU is common only to non-Ashkanazi Jews. In the Ashkanazi Jews PKU has not been detected although variants have been identified.^{36,37} Woolf⁵⁵ suggested that the variant disorders were a manifestation of the third allele for the PKU gene, but Hsia et al¹⁴ concluded that the variant disorder could be explained best by differences in modifier genes. Justice and coworkers⁵⁶ reported decreased liver phenylalanine hydroxylase activity in hyperphenylalaninemic patients (variants) and no activity in PKU patients. The latter findings suggest that the variant patients represent a "milder" form of PKU. Bessman,⁵⁷ however, has described an "isozyme" with the ability to metabolize phenylalanine. Woolf⁵⁸ has confirmed Bessman's findings of two separate protein fractions with phenylalanine hydroxylase activity in rat liver. Kaufman and Fisher⁵⁹ have published detailed findings of phenylalanine hydroxylase "isozymes." Kaufman⁶⁰ believes the decrease in phenylalanine hydroxylase activity in hyperphenylalaninemia (variants) is genetically determined. From these findings one could speculate that the variants have an isozyme which allows them to metabolize phenylalanine to an appreciable but lesser degree than normal.

A picture of the variant patient is beginning to emerge. Clinically, the majority are entirely normal. They have no distinguishing characteristic features. They do not, as a rule, have seizures, nor do they have abnormal electroencephalographic (EEG) patterns.⁶¹ This is decidedly different from untreated PKU patients, where as many as 75 to 95 percent of infants and children are reported to have abnormal EEG patterns.^{62,63} Biochemically, at times, the variants can be mistaken for PKU patients. Their serum phenylalanine levels may climb to as high as 75 mg per 100 ml⁵⁶ and often attain levels in the 30 to 40 mg per 100 ml range on an ordinary diet, but generally will not exceed 20 to 25 mg per 100 ml. In most instances the blood phenylalanine levels are less than 20 mg per 100 ml. The levels of urinary metabolites generally

are proportional to the elevation of the serum phenylalanine.²² Variant patients may excrete large quantities of PPYA; however, it is usually undetectable.²² Excretion of *o*-HPAA is usually increased only moderately—20 to 40 times normal—on an ordinary diet. However, it also can be present in greatly increased amounts.⁶⁴ One of the most striking characteristics of the variant is the fluctuation in the serum phenylalanine levels during sustained high intake of phenylalanine. The oscillations in the serum phenylalanine levels in addition to the responses to various kinds of loading studies suggest that the variants have some adaptive mechanism, possibly an inducible enzyme, or a modified enzyme.⁶⁵

Intellectually, the variant group seems to follow the distribution curve for the normal population. One of the authors (M.E.B.) is personally following 35 variant patients. All are developing in an entirely normal manner with the exception of two patients for whom another specific cause for retardation is known. Biochemically the phenylalanine tolerance tests of these infants and children are comparable to those determined on adult variant patients who also are intellectually normal in every respect.⁶⁶

Mental Retardation in PKU

As a consequence of the detection and recognition of variant patients, clinicians and investigators have been stimulated to look for causes other than elevated levels of phenylalanine to explain retardation in PKU. It is extremely difficult to ignore the experimental and neuropathological findings (see section on neuropathology) which are reported to be associated with high levels of blood phenylalanine. On the other hand, there are reports of patients who have been spared retardation despite very high blood levels of phenylalanine and significantly elevated levels of the urinary metabolites of PKU.⁶⁷⁻⁶⁹ Perry et al⁷⁰ described two siblings with identically elevated blood phenylalanine levels and characteristic urinary metabolites of PKU. One child was intellectually normal, the other profoundly retarded. Perry postulated that the decreased plasma glutamine level in the retarded child may have been the factor responsible for the retardation, since the concentrations of other metabolites and amino acids were comparable. There are reports which are in conflict with this hypothesis,⁷¹ and also reports which document abnormal levels of other plasma amino

acids in untreated severely retarded PKU patients.^{72,73} The possibility that some factor other than elevated blood phenylalanine is responsible for the retardation has long been considered. Fuller and Schuman⁷⁴ indicated that the ultimate intelligence in treated and untreated PKU is trimodal in distribution, which suggests that intelligence in PKU patients may be unrelated to phenylalanine levels. Retarded patients with low phenylalanine levels—less than 20 mg per 100 ml—have been reported.⁷⁵ Retardation in such cases could be due to causes other than PKU.

Wooley and Van der Hoeven⁷⁶ implied that the mental defect of phenylketonuria might be prevented by administering serotonin precursors. This contention is supported by the finding that blood serotonin levels are normal in variant patients but low in untreated patients with PKU.⁷⁷

Neuropathology

Poser and van Bogaert⁷⁸ in 1959, Malamud⁷⁹ in his report of eight cases in 1966, and more recently Crome and Pare⁸⁰ in their review and case reports of 1969 established the histologically variable and non-specific findings characteristic of PKU. Other investigators⁸¹⁻⁸⁴ have confirmed these variable findings, especially those of demyelination or defective development of myelin and the spongy lesions of the white matter as described by Malamud. Usually there is some decrease in brain weight. Most of these reports have emphasized the increasing degrees of myelin defect and spongy changes with increasing age in untreated patients. Evidence has been offered that dietary treatment may prevent these neuropathologic changes.^{81,85} The lack of findings in the treated patient reported by Salguero et al⁸¹ may have been because the patient was too young to show neuropathological changes and not because of treatment.

The structural alterations of the brain which increase with advancing age in untreated PKU are evidence of permanent damage. Likewise, with advancing age the mental defect associated with PKU becomes totally irreversible. In our experience other neurological manifestations of the disease, such as irritability, EEG changes and hyperactive behavior, are frequently reversible following dietary treatment even in older persons. Therefore, phenylalanine or one or more of its metabolites appears to have both reversible and irreversible effects.

Alterations in brain lipid metabolism in PKU which worsen with advancing age have been described recently in conjunction with permanent myelin and spongy changes. These lipid changes may be either the cause or the effect of the permanent neuropathologic damage. Analysis of brain tissue by Menkes,^{86,87} Gerstl et al⁸⁸ and Cumings et al⁸⁹ have shown reductions in total lipids, cholesterol, and certain proteolipids as well as alterations in composition and amounts of cerebroside and sulfatides. Lipid alterations have been variable but in most patients increase with increasing severity of histopathologic changes.

In the brain of a retarded child born of a phenylketonuric mother, Menkes and Aeberhard⁹⁰ found alterations in lipids and sulfatides similar to those found in PKU. The findings suggest that elevations of blood phenylalanine or its metabolites are toxic to the brain or interfere with normal brain development.

Neuropathologic studies of human material ordinarily present the late and static stages of PKU. Animal models of PKU have offered a research tool for investigation of the developmental and dynamic aspects of the neuropathologic features of this disease, and of the associated metabolic processes. Unfortunately, an animal model with a block in phenylalanine hydroxylation comparable to the metabolic error seen with human PKU does not exist. In neuropathologic and metabolic studies hyperphenylalaninemia is artificially produced by giving the animal large amounts of phenylalanine in the diet or by injection. The phenylalanine to tyrosine pathway is intact in these animals, and therefore the models not only have an artificially unbalanced hyperphenylalaninemia but also tyrosinemia. All studies have suffered from the fact that some of the changes seen may be reflections of imbalances of amino acids other than phenylalanine. Nevertheless, Chase and O'Brien⁹¹ have duplicated many of the pathologic findings of human PKU in infant rats that were made phenylketonuric experimentally. The brains of these rats were lighter than normal and the lipid and sulfatide contents were decreased. Of special interest in these studies was the finding that the first eight days of life was the most critical for normal brain development. The comparable period in humans occurs during the fetal stage. Winick's⁹² observation of the critical fetal period of brain growth partially explains the great risk of brain damage to infants born of phenylketonuric mothers. Ex-

periments have shown that in the developing animal high phenylalanine concentrations and deviations from an optimum ratio of essential amino acids results in impairment of protein synthesis.⁹³ Appel⁹⁴ has shown *in vitro* that phenylalanine can inhibit protein formation. Peterson and McKean⁹⁵ using brain homogenates demonstrated the same inhibition. Swaiman et al,⁹⁶ Aoki and Siegel,⁹⁷ Chase and O'Brien,⁹¹ and Longenecker et al⁹⁸ also have shown impaired protein synthesis in developing animals as a consequence of amino acid imbalances.

Decreased brain weight has been a common neuropathologic finding in human PKU. The finding by Chase and O'Brien⁹¹ of decreased amount of deoxyribonucleic acid (DNA) in developing brains of experimental PKU rats indicates impairment of cell division. Since the increase in the number of brain neuronal cells ceases at an early age in both the rat and man, permanent deficiency of cell number is a likely consequence of untreated PKU.

Dermatoglyphics

In 1965 Hirsch⁹⁹ reported abnormalities in the palm prints of PKU patients compared with controls. Alter¹⁰⁰ in 1967, in describing the dermatoglyphics of 100 PKU patients and 100 controls, did not confirm Hirsch's findings. He did find decreased frequency of whorls on fingers and an increase in the mean atd angle in affected females compared with control females. In attempting to reconcile the different findings of Hirsch and Alter, the differences in the frequency of palm print abnormalities seem more a difference between their control groups than between their PKU groups.

The questionable validity of Hirsch's controls, and the fact that differences in Alter's studies were limited to females, makes the findings of questionable significance. Certainly dermatoglyphic analysis would be of no assistance in diagnosing or screening for PKU.

Maternal PKU

Variables influencing the outcome in PKU are the concentration of phenylalanine and the age of the child when exposed to it. Subjects with temporary hyperphenylalaninemia and variants with blood levels of phenylalanine below 20 mg per 100 ml do not appear to be at great risk of intellectual deterioration.²² Patients with PKU may not have

TABLE 3.—Phenylketonuric Mothers and Their Children

Report	Mother			Status of Children			
	Date of Report	Age	I.Q.	Not Certain or Unreported	Normal	Retarded Non-PKU	PKU
Jervis (48)	1937	34	49	2			2
Jervis (48)	1937	50	50	1			
Jervis (107)	1939	27	60	1			
Jervis (108)	1954	—	High Grade	2			
Partington (111)	1962	36	102		1		2
Mabry et al (101)	1963	70	49			5	
Mabry et al (101)	1963	77	82	7		1	
Mabry et al (101)	1963	49	27			1	
Richards (124)	1964	70	50			3	
Coffelt (125)	1964	26	96*			2	
Forbes et al (126)	1966	—	*			1	
Allen (127)	1966	35	110			4	
Fisch et al (117)	1966	32	88			1	
Perry & Tishler (128)	1966	29	90			1	
Mabry et al (106)	1966	35	97			4	
Mabry et al (106)	1966	40	92			4	
Mabry et al (106)	1966	58	52	1		2	
De Menibus et al (129)	1967	—	—				
De Menibus et al (129)	1967	—	—	1		9	1
Colombo (130)	1967	35	90				3
Stevenson & Huntley (118)	1967	33	99	4		1	
Stevenson & Huntley (118)	1967	31	76	3		2	
Williams (120)	1968	—	62			4	
Waisman (110)	1968	—	94		1	3	
Allan & Brown (109)	1968	27	66		1	3	
Frankenburg et al (116)	1968	39	54			2	
Frankenburg et al (116)	1968	29	77			2	
Frankenburg et al (116)	1968	35	74			4	
Yu & O'Halloran (121)	1970	29	Borderline-dull normal			3	
						(2 PKU variants)	
Yu & O'Halloran (121)	1970	47	Mild-moderately retarded			6	
Totals	29			22	3	68	8

* Same mother.

significant intellectual deterioration even though allowed to have high blood levels after the age of six years. Probably little cerebral damage occurs with high serum phenylalanine levels even after three to four years. As indicated earlier, infancy appears to be a critical period for damage to occur from high phenylalanine levels. We could postulate that a fetus would be at even greater risk from excess phenylalanine exposure. Such an observation was supported by the report of Mabry et al¹⁰¹ which described seven non-PKU retarded children of three PKU mothers.

The fetus of the PKU mother may be exposed to blood phenylalanine levels higher than those in the blood circulating in the mother. Crumpler et al¹⁰² postulated and then showed that there is an active placental mechanism for maintaining higher fetal than maternal levels of amino acids. The mechanism apparently continues to operate even

with considerably elevated, artificially induced, phenylalanine levels in pregnant rhesus monkeys.^{103,104} Bessman¹⁰⁵ speculated that these findings are not due to an active placental mechanism, but rather due to an equilibration phenomenon—a rapid drop in the mother's levels and slow placental clearance.

In 1966 Mabry et al¹⁰⁶ reported three additional PKU mothers with 11 children, and summarized the known cases of PKU mothers at that time. In Table 3 Mabry's summary of cases has been brought up to date. The reports of normal children of PKU mothers by Jervis^{48,107,108} (listed by Mabry¹⁰⁶) did not describe the results of any formal psychometric evaluations or descriptions of the children's ability to cope. These cases therefore are listed as of uncertain status. Cases of maternal PKU published subsequent to Mabry's report have been added to give a total of 29 mothers with 101 chil-

dren. Eight of these children had PKU, and 22 are of uncertain status because the reports are incomplete or the child died in early infancy before evaluation could be done. This leaves 71 non-PKU children of PKU mothers, of which at the most three were normal and 68 were affected. The mother reported by Allan and Brown,¹⁰⁹ who gave birth to a normal infant, was treated with a low-phenylalanine diet after the fifth month of pregnancy. The status of two of the reported PKU mothers having the other reported normal children is questionable. In Waisman's¹¹⁰ case the mother's IQ was borderline—83. The mother in the family reported upon by Partington¹¹¹ was not a typical phenylketonuric. Her IQ was 102, and her fasting urine was negative by ferric chloride test and only faintly positive to Phenistix.[®] Her urine tests were strongly positive following a phenylalanine load; however, this may occur in PKU variants. Fasting phenylalanine blood levels on two occasions were 20.6 and 20.8 mg per 100 ml. Within a population of phenylketonurics such levels are low.⁵ The blood phenylalanine level one hour after loading was 37.2 mg per 100 ml on one occasion and 38.0 mg on another. Unfortunately, phenylalanine was not measured beyond four hours at either time. Therefore, a critical determinant of the variant disorder is missing (see earlier section, Variant Disorders).

Reports of retarded non-PKU children of PKU mothers frequently mention microcephaly, muscle hypertonicity, and hyperreflexia. Intrauterine growth retardation also is part of the syndrome.¹¹⁶⁻¹¹⁸ In addition to these findings and the intellectual defects, reports of anomalies in some of these children indicate that they may have a higher than normal risk of congenital defects of organ systems other than the central nervous system. These defects include a variety of congenital heart lesions,^{109,118-120} strabismus,^{118,121} clefts of upper eyelids,¹¹⁶ lipodermoids of cornea,¹¹⁶ hemivertebrae,¹¹⁶ spinal fusion in lumbar region,¹¹⁷ club foot,¹¹⁶ atrophic fingernails,¹¹⁶ congenital cataracts,¹⁰⁹ missing distal phalanx and bilateral incurved fifth fingers,¹¹⁶ dislocated hips,¹¹⁸ hydrocele,¹¹⁸ hypertelorism,¹²¹ epicanthic folds,¹⁰⁹ and mongoloid facies with normal chromosomes.¹²¹

There is no question that the risk of mental retardation or congenital anomalies in children born of mothers with PKU is extremely high and may even be 100 percent.

In contrast, infants born of variant mothers do

not appear to be in great risk of being retarded. The two mothers reported by Woolf et al¹¹² were, in light of current knowledge, probably variants and not phenylketonuric. Both mothers had phenylalanine levels below 10 mg per 100 ml. The six children of these two mothers were all normal. The mother reported by Onisawa et al¹¹³ was also a variant with blood phenylalanine levels ranging between 6 and 15 mg per 100 ml. She had a PKU child who was not treated with diet until 16 months of age. His severe mental retardation can be attributed to late initiation of dietary treatment. A second child, who had a blood phenylalanine level of 12 mg per 100 ml and a negative ferric chloride test, and therefore is probably a variant, received dietary treatment and is not retarded. A third child, reported as heterozygous for PKU, had normal intelligence. Lund and Ovalbøl¹¹⁴ also reported a variant mother who had one PKU child and one normal child. No formal psychometric testing of the normal child was reported, but development was normal during the first year of life. The mother had normal intelligence and blood phenylalanine levels ranging between 6 and 12 mg per 100 ml and up to 31 mg per 100 ml four hours after a phenylalanine load. Her urine was negative to ferric chloride except after loading. Among the cases reported by Kang and Paine¹¹⁵ was that of a mother with persistent hyperphenylalaninemia who appeared to be a variant. Although psychological test results were not reported, the child was said to be normal. The mother reported by Partington¹¹¹ also may have been a variant, and she also had a normal child.

We conclude from the reports of these few mothers with phenylalanine levels ranging up to 15 and 20 mg per 100 ml that variant mothers have only a slight risk of producing retarded infants.

Some PKU females treated from early infancy are now reaching childbearing age. Many of these girls have not received any dietary treatment for several years but have normal or near normal intelligence. They may now find a restricted diet—Lofenalac[®]—unpalatable; however, several of our teenaged PKU patients still prefer Lofenalac[®] to milk even though dietary restrictions were stopped several years ago.

Dietary treatment during pregnancy, even with ideal control, is associated with some risk of nutritional deficiency that could damage the fetus. We believe that, in general, PKU women should be advised against pregnancy. If they desire children,

then pregnancy should be planned so that dietary control is established before conception and extended throughout pregnancy. From our current knowledge of the favorable outcome of pregnancy in mothers with the variant disorder, it appears that it is probably safe for the blood phenylalanine levels to range between 10 and 15 mg per 100 ml. Allowing moderately elevated blood phenylalanine levels would decrease the risk of some unknown nutritional defect. To date, two PKU mothers have been treated successfully during pregnancy and have given birth to normal children.^{109,122} One of the mothers had blood phenylalanine levels up to 12.5 mg per 100 ml but repeatedly had positive reaction to tests for urinary PPKA.

Fisch et al¹²³ showed that mothers heterozygous for the PKU gene excreted greater than normal amounts of phenylalanine and its metabolites in breast milk. Postulating that PKU mothers (homozygous) would excrete even greater quantities, these investigators thought it inadvisable for such mothers to nurse their infants.

Behavioral Changes with PKU

Next to intellectual deficit, behavioral disturbance has been described as the most characteristic symptom of PKU. Hyperactivity, irritability, destructiveness, rage and fear reactions, and autistic behavior have been described repeatedly.^{108,131-134} In our experience, however, these behavioral abnormalities are frequent among mentally retarded populations in general, especially among those subjected to institutionalization, and are not specific for phenylketonurics.

More recently, Siegel et al¹³⁵ compared a group of PKU children with non-PKU matched controls on a school behavior rating scale. They found the PKU children more clumsy, talkative, and hypersensitive, but did not find that they differed significantly in hyperactivity. However, Johnson¹³⁶ in a study comparing a much larger group of PKU residents in institutions with a control group found the phenylketonurics significantly more hyperactive. He also found the PKU subjects rated higher than controls on the following behaviors: "self-destructive," "destroys clothing," "upsets furniture," "aggressive," "destroys ward property," "runs and paces," "attacks residents," "breaks windows," and "bangs doors when secluded."

The attention span of phenylketonurics, even those with mild mental retardation or normal in-

telligence, may be less than in persons without PKU.¹³⁷

From these reports and our own experience, we believe that retarded PKU patients, and even non-retarded or "borderline" PKU patients, not on a special diet, often have behavioral characteristics which make them a problem for parents and teachers. Hyperactive and destructive behavior is sometimes an indication for continuing dietary treatment beyond the age when no further intellectual deterioration is expected.

Some of the behavioral changes in PKU patients may be iatrogenic and not a result of the metabolic abnormality. Physicians must use caution and avoid being the cause of unnecessary psychological sequelae as a result of their investigations with these children. Sibinga et al¹³⁸ studied 30 PKU children, 16 of whom had experienced immobilization and sensory restriction during the first three years of life. Fourteen of these 16 had been in hospital during the first three years of life, whereas, only three of the 14 non-restricted PKU children had been. There was a significantly increased incidence of serious behavioral pathology as well as some decrease in intellectual level in the children experiencing immobilization and sensory restriction. Other variables between these PKU children appear to have been controlled. Many of the restricted children had been in hospital and restrained for metabolic studies, nine of them for three days or longer.

Wood et al¹³⁹ pointed out that learning in PKU children was curtailed by prohibitions against free explorations and the opportunity to make meaningful discriminations. These restrictions occurred because of the necessity of dietary control and the parents' reaction to the situation.

Psychopathologic Change in Relatives of Phenylketonurics

An increased incidence of psychopathologic conditions among parents and relatives of phenylketonurics has been reported in the older literature. More recent reports do not support this belief. Perry et al¹⁴⁰ surveyed a large number of relatives of PKU patients and a similar number of relatives of patients with Down's syndrome. No significant differences were found between the groups in incidence of psychosis, admissions to mental hospitals, personality disorders, chronic alcoholism, suicide, or criminal behavior. Larson

and Nyman¹⁴¹ compared the mental hospitalization and suicide rate of relatives of PKU patients with these rates in the general population and did not find significant differences. Blumenthal¹⁴² in a well-controlled study compared the parents of 108 phenylketonurics with the parents of 102 non-PKU retarded and of 121 children with cystic fibrosis. The parents of the PKU children did not differ from the other two groups when a standardized interview schedule was used to assess their mental health.

Dietary Treatment

The serum phenylalanine level at which treatment is warranted is speculative. Berman et al²² suggested that if the serum phenylalanine level remains at less than 20 mg per 100 ml on an ordinary diet, dietary treatment may not be needed. However, from the screening data provided by Guthrie,⁷⁵ there are retarded patients with serum phenylalanine levels below 20 mg per 100 ml. It is possible that their retardation is not related to hyperphenylalaninemia. It is also possible that their protein intake—they are in institutions—is low and the low serum phenylalanine values reflect this feature.

Such inconsistencies make it difficult to reconcile levels of phenylalanine and retardation. For this reason, many clinicians empirically treat all patients who have persistent hyperphenylalaninemia from any cause. Until there is a method for absolute diagnosis, perhaps at the enzyme level, or until it can be shown unequivocally that dietary treatment is not associated with improved development or more normal intelligence, most clinicians will continue to treat patients having significant hyperphenylalaninemia. Thirty-five years of intensive research has not determined the cause or causes of the retardation in PKU, and the precise reason for the efficacy of dietary treatment is yet to be found.

The increased detection of non-retarded persons with elevated phenylalanine levels has brought about reconsideration of the evidence for the effectiveness of treatment with low-phenylalanine diets. Despite severe criticisms of the research designs and interpretation of the data supporting the efficacy of dietary treatment,⁴³ most clinicians remain convinced, from empirical observations, that phenylalanine restriction is of value, especially in patients treated from early infancy.

Criticism of the evidence favoring dietary treatment has included these points:

- Comparisons made between treated and untreated groups included a selection bias. Untreated patients were first identified because of mental retardation, whereas most successfully treated patients were identified because of biochemical screening programs of newborns or as siblings of known phenylketonurics.

- Environmental factors have not been controlled. Some studies have included a disproportionately greater number of institutionalized retardates in untreated groups as compared with treated groups. Analyses of data have not recognized that patients receiving dietary treatment may receive a greater amount of parental time, stimulation, and attention than untreated patients and there is a placebo effect from the diet. Parents who maintain good dietary control compared with those who do not may be parents who are of higher intelligence and more capable of stimulating their children.

- Reports of treatment starting in the newborn period have included patients with hyperphenylalaninemia who would not have become mentally retarded in the natural course of their disorder.

- Invalid comparisons have been made between developmental tests in infancy and intelligence tests at older ages.

- "Blind" studies have not been done. The psychologists making developmental and intelligence tests knew which individuals were in diet-treated and control groups at the time of test administration.

- The restricted diet may be dangerous in some cases and lead to decreased intelligence through phenylalanine and protein deficiency.

A further difficulty in assessing the value of dietary treatment is that no center has had a sufficient number of cases to make statistically valid comparisons of the great number of variables leading to developmental differences. A Collaborative Study of Children Treated for Phenylketonuria, involving 18 centers distributed across the United States, was initiated by Dr. Richard Koeh of Childrens Hospital of Los Angeles in October, 1967, to answer many of these questions while considering the above objections.

Before any dietary treatment is begun, a diagnosis of PKU should be fairly firmly established. Hyperphenylalaninemia due to transient tyrosinemia should not be treated by phenylalanine re-

striction. Most investigators would not treat the variant disorders of hyperphenylalaninemia when the levels of serum phenylalanine remain consistently below 15 mg per 100 ml while the patient is receiving an ordinary diet. Many clinicians would not treat patients whose levels remained consistently below 20 mg per 100 ml and especially if the urinary metabolites of classical PKU were absent. If, however, the serum phenylalanine levels are persistently greater than 20 mg per 100 ml while the patient is ingesting an ordinary diet, it would be prudent to initiate dietary therapy. Periodically the patients should be restudied and "challenged" by tolerance tests to confirm the diagnosis. We suggest that this be done at four months, nine months, eighteen months and also at two to three years unless the diagnosis has been consistently reaffirmed by previous challenges.

Certain precautions must be observed when treating PKU. Practically all protein foods provide too much phenylalanine to meet both the protein needs and at the same time lower the serum phenylalanine levels in PKU patients. Specially prepared commercial products meet the above requirements. They are usually protein hydrolysates which have been modified and which can be obtained only with a prescription. In prescribing such a diet, the aim should be to meet the basic protein and caloric requirements and to give as much phenylalanine as can be tolerated while the blood phenylalanine level is maintained in the desired range. During infancy it is often difficult to conform to these requirements and at the same time give natural foods, but as many natural foods should be included as possible. This problem may soon be overcome. Bickel et al¹⁴³ have reported the successful treatment of PKU patients with a product prepared entirely from individual amino acids to which were added fats and vitamins. Because the mixture was entirely devoid of phenylalanine, many more natural foods could be given.

Clinicians at most treatment centers follow the Nutrition Research Council recommendations for proteins and calories¹⁴⁴ and attempt to maintain serum phenylalanine levels between 4 and 8 mg per 100 ml. The patient's blood phenylalanine levels must be monitored frequently to avoid subnormal levels. If the maximum amount of tolerated phenylalanine is given, there is little likelihood that a phenylalanine deficiency will occur. However, since the aim of treatment is to lower

the serum phenylalanine level, a critical point of phenylalanine restriction will be reached at which patients may go from an anabolic to a catabolic state. The levels of phenylalanine will decrease and then increase again as a reflection of these states and breakdown of tissue proteins.^{145,146} If one does not monitor frequently enough, or monitors blood phenylalanine levels only, there is a considerable likelihood that dietary treatment will not be optimal.

Initially, after the diagnosis is made and the serum phenylalanine level is being reduced by dietary restriction, serum phenylalanine levels should be monitored at least twice weekly. When the serum levels decrease to the recommended range, the levels should be checked weekly and ideally never at intervals longer than two weeks. If monitoring is done less frequently it is impossible to evaluate the quality of dietary control. Urine should be checked at three-month intervals for the metabolites of PKU. The urine reflects the quality of dietary control and also may show signs of a deficiency state. Often a catabolic state will be reflected by a mild to moderate generalized aminoaciduria. If the deficiency state is severe and persists for any length of time, especially in a young patient, growth and even intelligence may suffer. Not only must the phenylalanine needs be met, but also those for proteins, calories, fats, vitamins, and minerals.

The complications associated with dietary treatment have been reviewed by Hanley et al.¹⁴⁷ Signs associated with a deficiency state include: anorexia, diarrhea, anemia, hypoproteinemia, bone demineralization, rashes, hypoglycemia, seizures, and even death.

Length of necessary dietary and phenylalanine restriction is uncertain. Initially it was thought to be for the life time of the patient. We believe it is probably unnecessary beyond the age of six years for the prevention of retardation. Dietary restriction after six years may help prevent hyperactive behavior. Brain growth, as reflected by head circumference, approaches 90 percent of adult size by six years and myelination is also nearly completed by that time. Allen¹⁴⁸ routinely discontinues dietary restrictions by three years of age and has noted no deterioration in performance, EEG tracings or behavior in any of his patients. Ancillary to this are the reports of Fisch et al¹⁴⁹ who suggest that blood phenylalanine levels in the 10 to 12 mg per 100 ml range after

one year of age have little effect on the eventual intellectual outcome. This further supports Winick's⁹² data which suggests that the permanent number of brain cells is affected critically in the first six months after birth.

One must in the end make judgments about diet discontinuation for the individual patient. Seizures, hyperactivity, and deterioration in performance have been reported as guidelines in particular cases.^{150,151} Clayton et al¹⁵² suggested that EEG abnormalities provoked by an L-phenylalanine load are an indication for continuing dietary treatment. This may not be a useful criterion since EEG abnormalities have been provoked in control patients as a consequence of L-phenylalanine loading.¹⁵³ The question of diet discontinuation is much simpler for males than for females because of the problems of fetal malformations and retardation in untreated maternal PKU. It has been shown that PKU patients with normal IQ and with little evidence of damage are less likely to suffer further intellectual deterioration on reintroduction of normal diet than are patients who are damaged severely.¹⁵⁴

California Crippled Children's Service Program

Compulsory screening for PKU was implemented in California in 1966. The law and subsequent State Health Department regulations established that screening tests would be performed by regular licensed clinical laboratories and not in central state-owned or operated laboratories as is mandated in some states of the United States.³³ By the end of 1967, 179 laboratories distributed widely over the state had been approved for PKU screening tests.¹⁵⁵ Quality control in these laboratories is maintained by means of control specimens submitted to them regularly by the State Health Department.

A "fail-safe" system for follow-up of specimens found positive by screening is maintained through local health departments and the Bureau of Maternal and Child Health in the State Health Department. If a newborn's blood is positive (4 mg per 100 ml or greater) on screening, a second specimen is requested. After a second positive test, the infant should probably be referred for prompt diagnostic evaluation to a center approved by the Crippled Children's Service (ccs).

These centers provide initial treatment, follow-

up treatment, and consultations with physicians.¹⁵⁶ As a condition of approval these centers are required to provide the services of a multidisciplinary team, including a pediatrician expert in these problems, a psychologist, a social worker, a nutritionist, and a nurse. Complete laboratory capability for differential diagnosis of obscure metabolic diseases and their variations is also expected. All of these centers can when necessary call on a variety of other specialists such as geneticists, neurologists, child development experts, and experts in speech and hearing. As of the beginning of 1970, the following centers were approved for rendering these services to ccs: Childrens Hospital of Los Angeles, Orange County Medical Center, Los Angeles County-University of Southern California Medical Center, Children's Health Center at San Diego and Children's Hospital at San Francisco. Before 1970, certain individual pediatric specialists were approved for rendering diagnostic and management services under ccs support. These specialists continue to render some services to ccs-supported PKU patients and are in addition to the approved centers with complete teams.

In addition to original diagnostic evaluation for all patients needing such services, ccs will support continuing patient management, the required diet (Lofenalac[®]) and authorized consultations and re-evaluations for those patients determined to be in need of such support after financial screening. Continuing patient management may be supplied by physicians authorized to render such services in the local community with consultation or periodic re-evaluation being supplied by one of the approved centers. During the 1968-69 fiscal year, 107 children with the diagnosis of PKU were on the California ccs caseload.¹⁵⁷

The center concept has proven itself in California and elsewhere as being a very necessary corollary to mass screening programs. Clinicians at these centers usually can separate the severe from the mild forms of metabolic diseases and thus distinguish those variants not in need of treatment. Patients not in need of treatment thereby avoid expensive and at times dangerous dietary manipulations. The teams in these centers see enough patients to develop the experience needed to render the very carefully formulated counseling that the parents of these children always need. Support of a special diet for PKU patients through the ccs program is justified economically. The cost is small compared with the cost of years of

state hospitalization when severe brain damage is allowed to occur. From a humane point of view and family morale, if just one patient is kept from deteriorating, the state program is well justified.

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Current Concepts in the Treatment of Hypertension

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. EARLEY:* The topic for discussion this morning is current concepts in the treatment of hypertension. The case presentation will be given by Mr. Alan Hance of our fourth year class.

MR. HANCE:† This was the sixth admission to this hospital for a 63-year-old retired watchmaker, who was admitted from clinic because of uncontrolled hypertension. The patient had been known to have diabetes and hypertension for approximately ten years and had had numerous complications from severe peripheral vascular disease. In 1960 he presented with a clot at the iliac bifurcation, and a bilateral aorto-femoral bypass graft was placed. He was mildly hypertensive at that time. In 1961 he had a myocardial infarction and over the next four years several false aneurysms developed, necessitating revision of the grafts. In 1968 he had a complete bypass graft revision after admission for another false aneurysm. In 1969 the patient presented with dizziness and right arm weakness. Carotid arteriograms revealed bilateral

stenosis, intracranial, on the left. Right carotid endarterectomy was performed, and sodium warfarin (Coumadin®) was administered prophylactically. His blood pressure was well controlled on a regimen of reserpine and hydrochlorothiazide; the serum creatinine at that time was 1.5 mg per 100 ml. On a routine visit to hypertension clinic in April, 1970, his blood pressure was found to be out of control. Alphamethyldopa was administered, and subsequently the dosage of both alphamethyldopa and hydrochlorothiazide was increased but did not control his blood pressure. The patient began to complain of weakness, dry mouth and syncopal episodes. The serum creatinine rose to 3.2 mg per 100 ml. Three days before admission, ecchymoses developed on his left arm and buttock; Coumadin® was discontinued.

Vital signs on admission included supine blood pressure of 240/140 mm of mercury with an irregular pulse of 78 beats per minute. While he was standing, his blood pressure dropped to 120/80 mm, the pulse rate increased to 96, and he fainted.

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On physical examination the mucous membranes were dry; funduscopic examination revealed grade III hypertensive retinopathy; the cardiovascular examination showed forceful point of maximal impulse (PMI) in the sixth interspace at the midclavicular line. An S4 gallop was heard. Large ecchymoses were noted on the left forearm and buttoek.

Laboratory data included a white blood cell count of 15,000 per cu mm with a normal differential, hematocrit of 49 volumes percent, and hemoglobin of 15.8 grams per 100 ml. The specific gravity of the urine was 1.011, the pH was 7.5, four red cells and ten white cells were noted in each high-power field on microscopic examination. The serum sodium was 124, potassium 3.1, CO₂ 25, chloride 90; calcium and phosphorus were within normal limits. The serum uric acid was noted to be 12 mg per 100 ml, and blood volume determination showed significant volume contraction. An intravenous pyclogram showed poor filling but was otherwise unremarkable. The electrocardiogram showed left ventricular hypertrophy with frequent atrial and ventricular premature contractions. Because of the frequent premature contractions and hypokalemia, digoxin was discontinued. Volume depletion and hypokalemia were thought to contribute to his orthostatic hypotension, and diuretic therapy and salt restriction were discontinued. Six days after admission plasma volume was normal, and the patient had no further syncopal episodes. The antihypertensive medications were gradually increased, and he was discharged on a regimen of alpramethyldopa, 3 grams a day, hydralazine, 300 mg a day, and hydrochlorothiazide, 100 mg a day. With this treatment the blood pressure was adequately controlled. When the patient was recumbent, the blood pressure was 180/95; when he was standing his diastolic pressure was between 80 and 90. He was also placed on a diet with moderate salt restriction and was told to elevate the head of his bed.

DR. EARLEY: Dr. Kenneth Melmon, a recognized authority in the area of cardiovascular therapeutics, will discuss the problems involved in treatment of hypertension.

DR. MELMON: * This patient presented today illustrates some important and common problems in the management of hypertension. Sometimes risks in therapy must be taken, but they always should be balanced against the current informa-

tion that treatment of hypertension, regardless of its cause, is associated with improved prognosis.^{1,2}

Until two years ago it had not been documented that prognosis improved when blood pressure was decreased to normal from average diastolic pressures between 90 and 114 mm of mercury. However, the recent Veterans Administration study² has provided the clinician with very important information. When the treatment of elevated diastolic blood pressure is adequate, cerebral vascular accidents are decreased, and the deterioration of renal function is slowed. The one disappointing aspect of this study of efficacy is that the higher than usual rate of coronary disease, myocardial infarction and sudden death associated with hypertension^{1,2} are not altered by therapy.

Although we know a great deal about the pathogenesis of disease in patients with hypertension, in the majority of patients no known pathogenetic factor has been found that explains the unusual blood pressures. Thus, therapy may not be intellectually satisfying, but empirical therapy is nevertheless important and efficacious.

How do you go about choosing an antihypertensive agent? To some it may appear that we choose drugs at random, but convincing data indicates that there are reasons for selecting different agents. There are also important steps to be taken in evaluating the effects of the choice.^{3,4}

The challenge to the therapist treating the patient with hypertension is to lower blood pressure effectively without inducing symptoms or signs of compromised vital function (of the kidneys, heart or brain). This challenge must begin with a consideration of the physiological determinants of normal blood pressure and the sites at which drugs interfere with them, proceed to the mechanisms of action of antihypertensive drugs, and provide a plan that enables prediction of the consequences of a multiple drug regimen in a particular patient.

Physiological Regulation of Blood Pressure

Blood pressure normally remains remarkably constant despite changes in posture and wide variations in demand for blood flow to particular vascular beds, for example, skeletal muscle, the gastrointestinal tract, or the kidneys. Even during exercise dangerous swings in blood pressure are uncommon. Homeostatic mechanisms maintain the mean arterial pressure by controlling the car-

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ANATOMICAL EFFECTOR SITES FOR CONTROL OF BLOOD PRESSURE

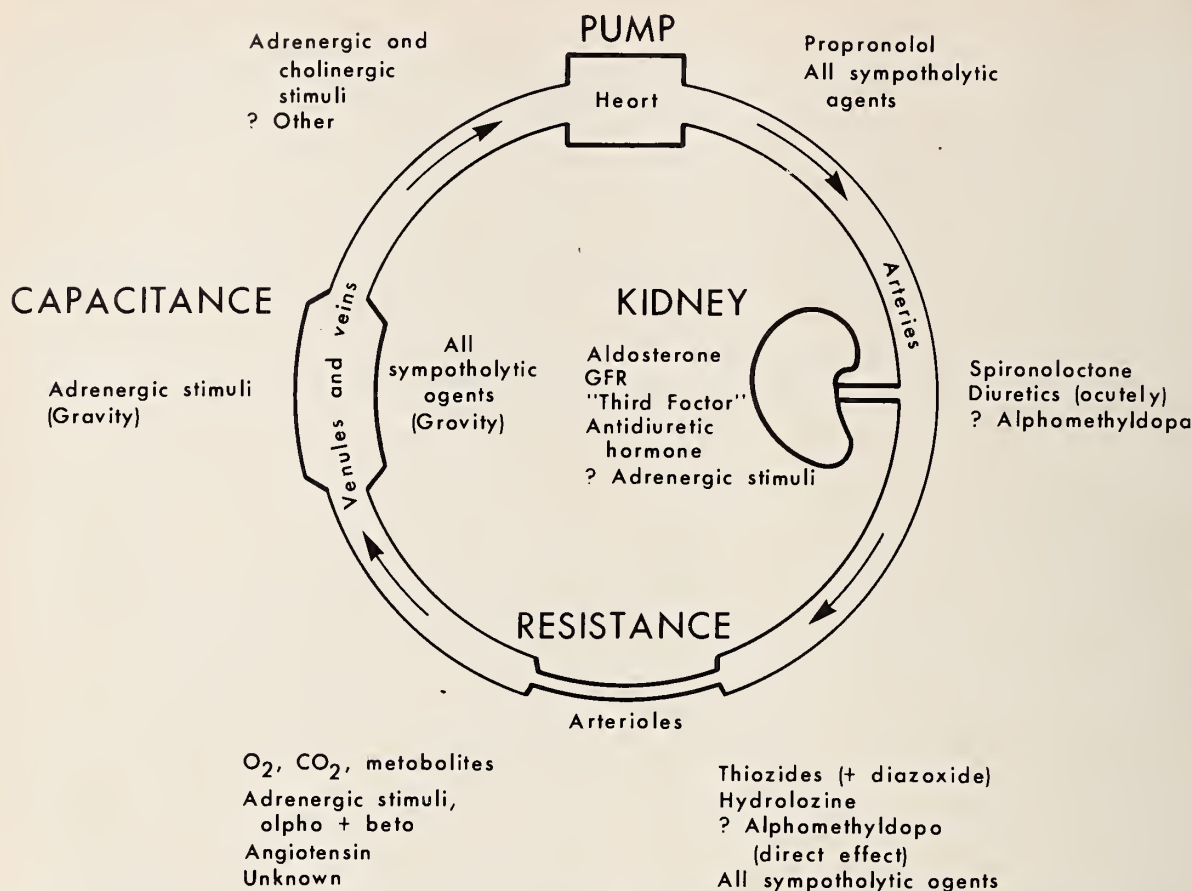


Chart 1.—Factors regulating blood pressure at four anatomic sites. Physiological influences acting on each site are listed on the left, pharmacological influences on the right. (Reprinted with permission of authors and publisher.³)

diac output and the peripheral vascular resistance. Minute to minute control of arterial pressure can be affected by a change in either of these factors. The blood pressure is directly proportional to the product of the amount of blood pumped into the arterial circuit per unit time and the resistance offered by peripheral arterioles to the flow of blood to the capillaries. An equally important influence on blood pressure is the total blood volume, which is an important determinant of cardiac output, hence, of blood pressure.

The homeostatic mechanisms controlling blood pressure work at four anatomic "effector sites" diagrammed in Chart 1:

- Peripheral arterioles or "resistance" vessels
- Venous "capacitance" vessels
- Heart
- Kidneys

Although the terms *resistance* and *capacitance* may seem new to the physician treating the hypertensive patient, they describe the functions of these vessels well and are in the common language of the cardiovascular pharmacologist. All useful antihypertensive agents act at one or more of these four sites.

Peripheral Arterioles. Although the primary lesion in essential hypertension appears to be a fixed increase in arteriolar resistance, none of the known physiological influences on the arterioles (listed in Chart 1) is deranged, and the biochemical basis of the increased vascular resistance has not been defined. Evidence suggests that changes in vessels that are responsible for peripheral resistance serve chiefly to redistribute the blood flow to regional vascular beds in response to increased local demand for oxygen or energy substrates.

Except in hypovolemia, changes in constrictor tone of systemic arterioles are not important in maintaining the arterial blood pressure during changes in posture. Changes in the peripheral resistance are mediated by autoregulatory influences (for example, pO_2 , pCO_2 , endogenous metabolites), the actions of the sympathetic nervous system, or the effects of angiotensin, a circulating peptide produced by the enzymatic action of renin on a plasma globulin.

Venous Capacitance Vessels. When the sympathetic nervous system is stimulated, peripheral venules constrict, producing a transient increase in the amount of blood returning to the right atrium. Thus, baroreceptor reflexes can augment cardiac output and maintain blood pressure, independently of direct autonomic influences on the heart. Both normal and hypertensive men depend more on constriction of capacitance vessels to maintain blood pressure during normal activity than on adrenergic control of arteriolar resistance. Accordingly, a powerful sympatholytic drug which diminishes venous return will produce a relatively great decrease in cardiac output. The effect on blood pressure will be most prominent when the patient is sitting or standing because gravity then causes blood to pool in dependent venous beds.

There are a variety of ways to evaluate the effects of drugs which primarily act on the autonomic nervous system. One way that was used in today's presentation was to stand the patient up to see whether he would fall. Such a procedure is not as sensitive a tool as we would like to use.

One of the best bedside methods used to test autonomic nervous reflexes is to observe the patient during and after a Valsalva maneuver.⁵ There will be a rapid decrease in flow to the right side of the heart, a pronounced decrease in stroke volume and a baroreceptor response which (if the autonomic nervous system is intact and functional) leads to tachycardia while the blood pressure is falling. When the glottal pressure of the Valsalva maneuver is released, blood flow to the heart returns, and there is an overshoot in blood pressure subsequently, followed by a few beats of bradycardia. If the bradycardia or the blood pressure overshoot is absent, we have evidence that the drug has affected the autonomic nervous system. If response to the Valsalva maneuver is normal, drug effect is inadequate regardless of the dose of drug administered. Lacking that evidence or deciding not to look for evidence

of autonomic insufficiency when using an anti-autonomic drug is to ignore a major clinical objective in drug administration. Assessing the progress of orthostatic hypotension and tachycardia may be another way of determining the degree of autonomic insufficiency produced by a drug like guanethidine, but simultaneous changes in blood volume may also contribute to the response to standing.⁵

Heart. During exercise, and to a lesser extent when the upright posture is assumed, baroreceptor reflexes induce increased sympathetic and decreased parasympathetic stimulation of the heart. The resulting increase in heart rate and contractility contributes to a rise in cardiac output.

Volume. The total blood volume normally remains constant during wide variations of salt and water intake. This is achieved by control of water intake and by variation in renal reabsorption of sodium and water. Decreased renal blood flow due to hypotension or hypovolemia triggers secretion of renin by the kidneys. Renin acts through increased plasma concentrations of angiotensin to stimulate adrenal secretion of aldosterone, which in turn promotes reabsorption of sodium by the distal convoluted tubule of the kidney. Increased renal perfusion will reduce renin release and consequently aldosterone secretion. This control system is essential for the maintenance of a constant blood volume. An acute fall in the glomerular filtration rate causes an increase in fractional reabsorption of filtered sodium; an increase in the glomerular filtration rate has the opposite effect. A controversial "third factor" has been invoked to explain the appropriate natriuresis that occurs in response to a sodium load in animals in which the other two "factors" are kept constant (that is, with maximally effective doses of exogenous mineralocorticoids and constant glomerular filtration rate). The "third factor" may be a circulating natriuretic hormone or the result of intrarenal redistribution of blood flow, or both.

All four "effector sites" (peripheral arterioles, venous capacitance vessels, heart, kidneys) must remain intact and normally responsive for homeostasis of blood pressure. Moderate functional impairment at one site may not result in changes in blood pressure when the subject is at rest, but cardiovascular stress or impaired function at a second site is likely to produce abnormalities in blood pressure.

Classification of Antihypertensive Agents

All currently available antihypertensive agents act by impairing normal homeostatic mechanisms. The efficacy and much of the potential toxicity of antihypertensive regimens can be predicted if drugs are considered in relation to the homeostatic effector sites on which they act (Chart 1). At a previous Grand Rounds we discussed the pharmacologic features of most of the drugs.⁶ Today we will attempt to classify them according to the sites on which they exert their most important therapeutic effect.

The thiazide diuretics hydralazine and diazoxide directly relax arteriolar smooth muscle. These drugs do not affect sympathetic reflexes and therefore produce little or no postural or exercise-induced hypotension. Unfortunately, when used alone, most of these drugs are not effective in doses that are not also toxic. Diazoxide is an exception to this rule and is useful for treatment of severe or accelerated hypertension, but must be administered intravenously and for a short duration.

Methyldopa (Aldomet®), generally considered a sympatholytic drug, also directly dilates resistance vessels. Such an action, in addition to its central nervous system effects, might account for the fact that methyldopa produced a considerably greater decrease in supine blood pressure than guanethidine or pargyline, which act mainly by impairing the sympathetic reflex function of capacitance vessels.⁷ Parenteral reserpine may reach sufficient concentration in the blood to dilate peripheral resistance vessels directly. This action is independent of the sympatholytic effect of oral reserpine. A word about the parenteral use of these agents seems justified at this point. Inasmuch as parenteral reserpine can directly decrease peripheral resistance when administered in high concentrations, it is an attractive agent for use in patients with malignant hypertension.

Why, then, has reserpine fallen into a certain amount of disrepute in the treatment of malignant hypertension? It is not because the drug is ineffective or necessarily has inconsistent action. Rather, it is probable that its effects are erratic only when we are not using the drug properly. In patients with accelerating hypertension it is likely that blood flow to subcutaneous tissue and muscle is inconsistent. Therefore, if the drug is administered into a site of relatively poor blood

flow, little effect will be seen. If it is administered into a site in which flow is active, an inordinate response may result from a standard dose. When we deal with an extremely severe disease, we cannot afford to take the chance of using a drug that either produces an inordinate response or no response at all. Conversely a standard technique could be developed for intravenous administration which would avoid any variances in absorption.

Drugs that Impair the Reflex Function of Capacitance Vessels. All the drugs in this group, which includes the most commonly used antihypertensive agents, act by inhibiting the sympathetic nervous system (Chart 2). They produce some fall in peripheral vascular resistance and affect myocardial function, but their predominant hypotensive effect depends upon inhibition of the capacitance vessels. They lower blood pressure most effectively when the patient is sitting, standing or exercising—the situations in which sympathetic tone is usually called upon to constrict capacitance vessels and increase venous return of blood to the heart. Hence it is not surprising that postural hypotension is the chief disadvantage of their use.

The mechanisms by which these drugs inhibit sympathetic function must be considered in planning a therapeutic regimen. The drugs fall into three sub-groups: (1) Drugs which produce direct effects on the postganglionic adrenergic neuron; (2) alpha-adrenergic blocking agents; and (3) ganglionic blockers.

1. Drugs which produce direct effects on the postganglionic adrenergic neuron: Reserpine is effective in treating mild to moderate hypertension. Its chief limitation in therapy is the wide variety of toxic effects that are likely to appear before satisfactory hypotensive effects are achieved. These include nasal stuffiness, a tendency to duodenal and gastric peptic ulceration, impaired ejaculation, postural hypotension, and a high incidence of mental depression which may be irreversible and has led to suicide.

Methyldopa is also effective in patients with moderate hypertension. The usual practical therapeutic limitations are the drug's relative impotence in severely hypertensive patients, the development of tachyphylaxis in patients with mild disease, and the need to take large numbers of tablets every day. For practical purposes, if 3 grams of methyldopa does not control the blood

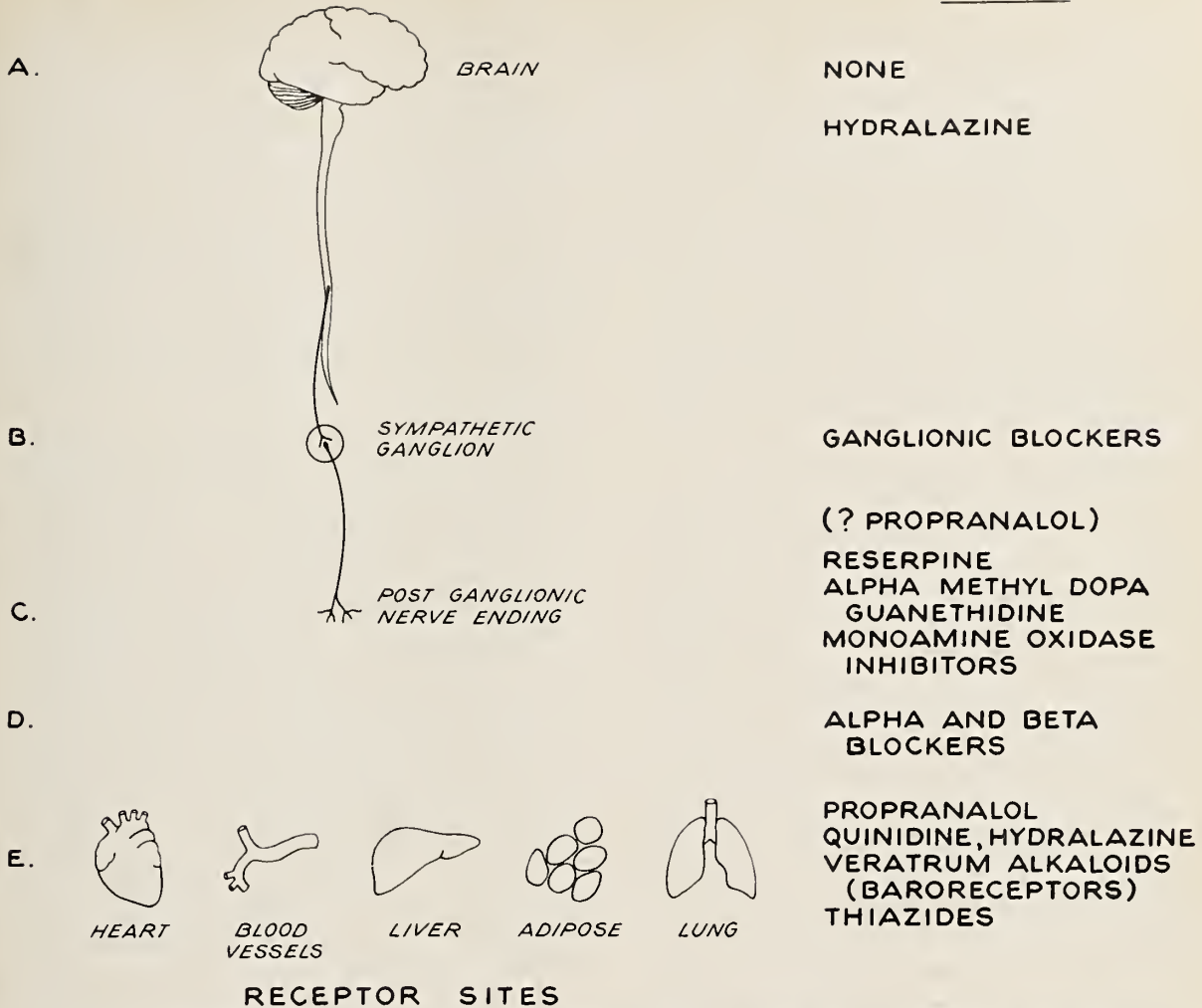


Chart 2.—Schematic representation of various anatomical levels at which antihypertensive drugs may work. A. Central Nervous System. B. Sympathetic and Parasympathetic Ganglia. C. Postganglionic Nerve Body. D. Postganglionic Nerve Ending. E. Effector Sites for Catecholamines. (Reprinted with permission of authors and publisher.)

pressure, alternate or additional drugs should be considered. Toxic effects include sedation (which usually subsides while administration is continued), impaired ejaculation, and orthostatic hypotension. In a large proportion of patients a reversible positive reaction to the Coombs test develops during long-term therapy, but hemolytic anemia due to the drug is rare.

Guanethidine (Ismelin®) is a basic agent that does not readily cross the blood-brain barrier, and it therefore does not produce undesirable central nervous system effects. Guanethidine works exclusively by interference with postganglionic nerve activity. Its therapeutic and toxic effects (as opposed to reserpine and alphas-

ynldopa) rely on exactly the same actions. Overdose produces increasingly profound autonomic insufficiency which, although efficacious, is intolerable and dangerous. The drug must enter the postganglionic nerve ending; and, when it does, it initially displaces the ordinary concentrations of the nerve endings' transmitter, norepinephrine. In addition, it prevents further release of catecholamines remaining within that ending.

If an overdose of guanethidine is administered, a paradoxical *hypertensive* response may occur. The blood pressure may rise because of the dose-dependent rate of release of the catecholamines. In these circumstances, phentolamine, an alpha blocker, which ordinarily would not be used in

the management of essential hypertension, becomes the primary antidote. There are two challenges in such a setting. First, the physician must recognize that he may have caused the increase in blood pressure and not just interpret the event as an unexplained exacerbation of the disease state. Secondly, he must also understand the pharmacological activity of the drug and administer the antidote. If guanethidine fails to produce a response, the cause may be related to its mechanism of action. If such drugs as imipramine hydrochloride (Tofranil®) and amitriptyline hydrochloride (Elavil®), which prevent guanethidine's entrance into nerve tissue, are being used, no decrease in blood pressure will be observed.

A third important clinical consideration related to the effects of guanethidine is associated with its pharmacokinetic features. After standard doses have been administered, considerable time elapses before its effect is seen. Therefore, it takes a considerable time to evaluate the effects of change of any dosage regimen. The half-life of guanethidine is approximately three days. Until at least three to five half-lives have passed, a change in the dose will not be fully appreciated.⁸ Therefore, one cannot give a patient a standard dosage of guanethidine and be satisfied with a fall in pressure at the end of five to six days. One must realize that the effects of the drug regimen will not plateau that quickly and that gross toxicity may occur within two weeks. This concept of time delay before maximal effects are seen is important both in increasing and in decreasing the repeated dose of the drug or changing intervals between doses.

Inhibitors of monoamine oxidase, such as pargyline (Eutonyl®), can be effective antihypertensive agents, but are presently of more theoretical than practical interest because of serious toxic reactions, including interactions with other drugs.

2. Alpha-adrenergic blocking agents: Phentolamine (Regitine®) and phenoxybenzamine block the effect of norepinephrine at postsynaptic receptor sites. Since the blockade is most effective when the blood concentration of endogenous catecholamines is high, these drugs are most useful in the diagnosis and treatment of pheochromocytoma. Phenoxybenzamine must be metabolized before it is active and, therefore, has a slower onset of action than phentolamine; but its

duration of action is longer. Neither drug is useful in the treatment of essential hypertension.

3. Ganglionic blockers: Agents that inhibit synaptic transmission at autonomic ganglia are effective sympatholytic agents—for example, trimethaphan (Arfonad®), pentolinium (Ansolyse®), mecamylamine (Inversine®). Unfortunately, they are also toxic because the sympatholysis is so complete and because they inhibit parasympathetic function as well. Accordingly, these drugs are useful only in very severe, or accelerated, hypertension when their toxicity can be tolerated for short periods to achieve the desired effect.

Drugs with a Direct Action on the Heart. The ordinary sympathetic activity that contributes to heart rate and myocardial contractility can be blocked by sympatholytic drugs, although these drugs depress cardiac output (and, therefore, blood pressure) primarily by decreasing venous return to the heart. Only the beta-adrenergic blocking agents, such as propranolol (Inderal®), lower blood pressure by a selective and predominant effect on the heart itself. In addition to its beta-blocking activity, propranolol may be a myocardial depressant. Since one of the primary goals of antihypertensive therapy is to prevent later cardiac decompensation, the rationale for use of such a drug may be questioned. When used alone, propranolol has not been an effective antihypertensive agent. Its usefulness in combination with other agents is now being evaluated. In the patient we are discussing today it is contraindicated, as he was taking tolbutamide. We know that sympathetic reflexes are important in compensating for any extraordinary hypoglycemia that might occur. Thus, in the presence of beta-blocking agents, tolbutamide could become an extremely toxic agent.

Drugs That Decrease Blood Volume. Decreasing blood volume is certainly feasible, but it is impractical as a means of controlling hypertension. A decrease in blood volume sufficient to reduce blood pressure could compromise perfusion of vital organs. Spironolactone (Aldactone®), which antagonizes the aldosterone effect on renal sodium absorption, is a relatively ineffective antihypertensive agent (except, of course, in primary hyperaldosteronism). The acute antihypertensive effect of the thiazide diuretics is partly due to the net loss of salt and water they produce. The hypotensive effect, however, may per-

sist after total body sodium and blood volume have returned to normal. In animals, methyldopa may reduce renin secretion (and, hence, aldosterone secretion and distal tubular sodium reabsorption). The relative importance of this effect in treating hypertension in man is not clear.

Goals and Limitations of Therapy in Individual Patients

The ultimate goal of preventing morbidity and death from hypertension is to lower the blood pressure to acceptable levels and keep it there. Before beginning treatment, the physician must decide exactly what blood pressure is "acceptable," how rapidly that level must be reached, and what kinds and degree of toxicity can be risked in the patient. These decisions depend upon indispensable information as to the severity of the patient's hypertension and the presence of factors that may modify drug response or toxicity.

Severity of Hypertension. The absolute level and constancy of the elevated blood pressure are obviously important. An equally important index of severity is the presence and degree of damage to target organs such as the heart, brain, retina, kidneys, and peripheral vasculature. Mild hypertension is present when the diastolic blood pressure is consistently between 90 and 115 mm of mercury in the absence of target organ damage. Moderate hypertension consists of a diastolic blood pressure of 115 to 130 mm with or without mild impairment of target organ function. Hypertension is severe when diastolic blood pressure exceeds 130 mm or when evidence of more pronounced damage to target organs is present. These gradations of severity correlate very well with prognosis and should help determine the intensity and acceptable risk of toxicity. Acceleration in the rise in blood pressure or degree of organ damage (especially papilledema) carries an extremely grave prognosis, and constitutes the therapeutic emergency we call "accelerated" or "malignant" hypertension.

Factors That May Modify Drug Response or Toxicity. The patient's previous response to antihypertensive drugs may be of value in predicting beneficial or toxic effects of a new regimen. Age should always be considered in determining the intensity of a hypotensive regimen, because older patients without overt disease tend to have higher diastolic and systolic blood pressure than younger patients, and cerebral arteriosclerosis and

decreased renal function may make older patients more sensitive to drug-induced decreases in blood pressure. Thus, the blood pressure level aimed at may be higher in these patients. The younger hypertensive patient has a potentially greater life span and, therefore, has much more to gain from control of high blood pressure than the older patient. Since the prognosis is considerably better for women than for men, the patient's sex may also be an index of the relative need for intensive treatment.

In some instances, the patient's occupation and level of ordinary physical activity may make a mild loss of "zip" due to reserpine intolerable, while use of sympatholytic drugs may predispose the active patient to postexercise syncope. Psychiatric status should always be evaluated, as signs of mental depression may preclude the use of reserpine or other drugs that enter the central nervous system. Additionally, the physician should ask the patient about the use of psychotropic drugs that may interact with many antihypertensive drugs.

The physician should always ascertain whether the patient will take the drugs he prescribes. Approximately half the hypertensive men selected for a well-designed trial of antihypertensive therapy had to be dropped from the study because they did not take medication.^{1,2} Unless the therapist considers the possibility of noncompliance, he is likely to prescribe "escalating" doses of more and more potent antihypertensive agents when the blood pressure remains elevated despite putative treatment.

Rational Combinations of Antihypertensive Drugs

In contrast to treatment of many other diseases, the treatment of hypertension with more than one drug ("polypharmacy") is theoretically sound and usually necessary. Polypharmacy is necessary because in most patients no drug can produce sustained decreases in blood pressure without also provoking considerable toxicity. Since a number of antihypertensive drugs work by different mechanisms, they can be combined in an effective regimen with diminution in overall toxicity.

Once reasonable therapeutic goals have been determined, the physician is ready to plan a drug regimen. In order to make rational predictions of the efficacy or toxicity of a particular drug (or

of a combination) he must consider the "effector site," or sites, and the mechanism of action of each hypotensive agent. The mainstay of therapy, but not necessarily the first drug given to the patient, is usually a sympatholytic agent. Reserpine or methyldopa can usually control mild hypertension; however, guanethidine is often necessary to control more severe hypertension. For accelerated or malignant hypertension, immediate treatment in the form of a fast-acting ganglionic blocking agent may be necessary.

Because of the importance of the sympathetic nervous system for homeostasis of blood pressure, sympatholytic drugs are the most effective antihypertensive agents, particularly in ambulatory patients. Since the principal effector site for these drugs is the venous capacitance bed, they are relatively ineffective when the patient is supine (less venous pooling due to gravity). This explains why sympatholytic drugs must usually be used in combination with other drugs acting on different effector sites. If control of supine blood pressure rests entirely upon inhibition of sympathetic function, orthostatic hypotension is almost inevitable.

Rational Combination of a Sympatholytic Agent with a Drug Acting Directly on Arterioles. The chief limitation of the thiazides and hydralazine is that they are relatively weak antihypertensive agents when used alone in acceptably safe doses. By itself chlorothiazide (Diuril®) is unlikely to reduce elevated blood pressure to acceptable levels, but it can reduce the dose of any sympatholytic agent necessary to achieve a given decrease in both supine and standing blood pressure. Since chlorothiazide acts at a different site than reserpine, it may render reserpine effective at doses below those that produce mental depression, or allow the use of methyldopa or guanethidine at doses that produce little postural hypotension.

Rational Addition of Hydralazine to a Regimen. In one therapeutic trial the combination of reserpine, chlorothiazide, and hydralazine produced a significant decrease in blood pressure, morbidity, and death in men with moderately severe hypertension.¹ The addition of hydralazine to reserpine and chlorothiazide was rational because none of the peripheral vasodilators produces the maximal possible effect; hence, their individual effects can be additive. The combination also allowed hydralazine to be used at doses

that were less likely to produce a dose-related toxic effect: the syndrome resembling systemic lupus erythematosus.

Irrational Combination of Two Sympatholytic Drugs. In sufficient doses, guanethidine produces nearly maximal sympathetic blockade. Consequently, it should in general replace, not be added to, drugs such as reserpine and methyldopa when they have proved ineffective. Furthermore, these drugs probably all act on the postganglionic adrenergic neuron, and theoretically may antagonize one another's effects. Reserpine, for example, causes release of guanethidine stored in adrenergic neurons and might be expected to decrease its effect. One exception to this rule might be the combination of a rapidly acting ganglioplegic drug, such as trimethaphan, with a potent sympatholytic drug like guanethidine in the treatment of malignant hypertension. This combination is defensible if immediate control of blood pressure is required, since in ordinary doses by the oral route guanethidine requires at least three days to produce a useful antihypertensive effect.

Other Therapeutic Maneuvers. If the actions of therapeutic maneuvers on "effector sites" that control blood pressure are considered, then it is possible to decide which ones are rational. Salt restriction is not likely to augment the hypotensive effect of the thiazide diuretics and may increase the likelihood of hypokalemia or hypovolemia. Orthostatic posture, on the other hand, should increase the effect of sympatholytic agents since both maneuvers decrease cardiac output by causing blood to pool in capacitance vessels. Patients whose standing blood pressure is well controlled with guanethidine, for example, may be hypertensive when supine. In these patients elevation of the head of the bed may make guanethidine effective throughout the entire 24 hours. In an emergency situation, the full hypotensive effect of a ganglionic blocking agent cannot be achieved unless the head of the patient's bed is elevated.

Drug Combinations to Be Avoided

Monoamine Oxidase Inhibitors with Almost Any Other Drug. Drugs which release norepinephrine (such as reserpine, guanethidine, methyldopa) or tyramine (contained in many foods) may provoke hypertensive crises, fever, or cardiovascular collapse in patients receiving mono-

amine oxidase inhibitors. The hypertension is due to augmented release of norepinephrine and should be treated with the rapidly acting alpha-adrenergic blocking agent, phentolamine.

Guanethidine with Amphetamines or the Tricyclic Antidepressants. Both amphetamines and tricyclic antidepressants (Tofranil® and Elavil®) block the entry of guanethidine into the sympathetic neuron making control of blood pressure difficult and occasionally precipitate acceleration of hypertension.

It should be noted that perfect understanding of circulatory physiology and the pharmacology of antihypertensive drugs will not alone produce effective therapy. When rationally determined goals have been set, appropriate drugs prescribed, and the drugs administered in adequate doses to produce their maximal effect (irrespective of the drug brochure), the results of treatment must still be carefully measured and evidence of toxicity must be actively sought. Without careful observation, changes in a therapeutic regimen are unlikely to lead to increased efficacy. For example, the dose of a sympatholytic drug should not be changed (or discontinued) unless the presence or absence of a sympatholytic effect in the patient has been documented, since sympathetic inhibition may be the chief or only means by which the drug could possibly lower blood pressure. If no sympathetic inhibition has been demonstrated and there is no intolerable toxicity, a 1.5 gm daily administration of methyldopa should not be discarded in favor of guanethidine. The reason is that an antisympathetic effect coupled with effective lowering of blood pressure may be achieved with higher doses of meth-

yldopa. Clinical assessment of sympathetic function is possible at the bedside by measuring the response to Valsalva's maneuver and orthostatic changes in blood pressure and pulse rate.⁵ Thus, it can be clearly seen that knowledge of the pharmacology of antihypertensive drugs can be of great help to the physician when he outlines the treatment of his hypertensive patients.

TRADE AND GENERIC NAMES OF DRUGS

Coumadin®sodium warfarin
Aldomet®methyldopa
Ismelin®guanethidine
Tofranil®imipramine hydrochloride
Elavil®amitriptyline hydrochloride
Eutonyl®pargyline
Regitine®phenolamine
Arfonad®trimethaphan
Ansolysen®pentolinium
Inversine®mecamylamine
Inderal®propranolol
Aldactone®spironolactone
Diuril®chlorothiazide

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HYPERFUNCTIONING THYROID ADENOMAS

"The clinical manifestations of hyperfunctioning thyroid adenomas develop insidiously and frequently go unrecognized until some overt event such as atrial fibrillation calls attention to the basic disorder. Hyperfunctioning adenomas are found most frequently in women over the age of 30 but may occur in men and also in younger age groups. Nervousness, irritability, loss of weight, and excessive appetite may be present, but not strikingly so, as is common in Graves' disease. Mild heart failure, cardiac arrhythmias, tachycardia, and a high pulse pressure are more common findings. Eye signs are notably absent in patients with hyperfunctioning adenomas. If they are found, the patient more than likely has Graves' disease and the adenoma is incidental."

—WILLIAM D. HOLDEN, M.D., Cleveland
Extracted from *Audio-Digest Surgery*, Vol. 17, No. 1, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057

Important Advances in Clinical Medicine

Epitomes of Progress -- Pediatrics

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Pediatrics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Pediatrics which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pediatrics of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

Dialysis and Homotransplantation In Children

For a number of years after the initiation of hemodialysis and renal transplantation there was a widely held prejudice against using these procedures for infants and children. During the past three to four years, the experience from several centers indicate that the pediatric patient is a favorable recipient in spite of special problems imposed by the necessity for immunosuppression during the period of growth and maturation.

A review of the survival data in patients under 16 years of age receiving consanguineous renal transplants indicates that the one-year survival is approximately 80 percent, which is similar to the experience in adults receiving kidneys from related donors. The results of the reported studies therefore indicate that renal homotransplantation is an acceptable therapeutic procedure for end-stage renal disease in children. Special attention, however, must be given to the psychologic, social, and emotional aspects of patient care in a program for renal homotransplantation in children.

FRED G. SMITH, JR., M.D.

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Lilly JR, Giles G, Hurwitz R, et al: Renal homotransplantation in pediatric patients. *Pediatrics* 47:548-557, Mar 1971

Developmental Biochemistry Of the Intestine

During development, the small intestine undergoes many enzymological and physiological alterations in preparing the human fetus for extrauterine life. Glucose and l-amino acids are actively transported by the twelfth week of fetal life. Activities of intestinal alkaline phosphatase, proteases, dipeptidases and disaccharidases are detectable in the ten-week fetus and increase rapidly after the twelfth week. Maltase and lactase increase more slowly, but are developed by the 28th week of fetal life.

Pancreatic proteolytic enzymes are active after the fifth month, and lipase activity is developed by the seventh month of fetal life. Pancreatic amylase is barely detectable at term, but increases rapidly during early post-natal life. Except for certain saturated fats and starches, the human fetus is able to digest and absorb most nutrients by the 28th week of gestation.

PHILIP SUNSHINE, M.D.

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- Herbst JJ, Sunshine P, Kretchmer N: Intestinal malabsorption in infancy and childhood. *Advances Pediatr* 16:11-64, 1969

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) refers to the activation of the coagulation mechanism within the circulation with deposition of fibrin in the vascular periphery. When extensive, it has two severe effects: (1) It may consume coagulation factors so rapidly that an acquired

bleeding disorder develops, characterized by hypo- or afibrinogenemia (defibrination), thrombocytopenia, and low levels of factors II, V, and VIII; and (2) it may interfere with peripheral blood flow with resultant tissue damage. Severe DIC with defibrination may occur in a variety of disorders, such as bacterial sepsis, certain viral, fungal and rickettsial infections, hemolytic transfusion reactions, hemangiomas, snake bites, malignancies (neuroblastoma, leukemia), and obstetrical emergencies (placenta previa, abruptio placentae).

Laboratory tests of value in the diagnosis of DIC are prolongation of the thrombin and partial thromboplastin times, low levels of factors I (fibrinogen), II, V, VIII and platelets, and elevated levels of fibrin split products in the serum (as a result of secondary fibrinolysis of deposited fibrin). For most clinical situations, hypofibrinogenemia (fibrinogen less than 150 mg per 100 ml) and thrombocytopenia (platelets fewer than 100,000 per cu mm) are the two most characteristic laboratory abnormalities.

Treatment of severe DIC is initially aimed at removing the stimulus for coagulation by prompt treatment of the underlying disease (for example, antibiotics for infections). The decision to use heparin to prevent further fibrin deposition is dependent on: (1) The likelihood of continuing intravascular coagulation, and (2) the degree of tissue damage already present. Thus, if the etiology of the DIC is such that interruption of the process cannot be immediately accomplished (for example, in a viral disease) or if there is a grave risk of loss of soft tissue or extremities with additional thrombosis, heparin therapy should be instituted.

Other supportive therapy may include intravenous fluids for circulation support, fresh blood, fresh or fresh-frozen plasma or fibrinogen for bleeding, and low molecular weight dextran for excessive tissue destruction.

E. RICHARD STIEHM, M.D.

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Antiviral Therapy in Abnormally Susceptible Patients

A recent report, as well as our own experience with varicella in a child with leukemia, indicates an area of therapy that, at the moment, seems promising. In the past two years the clinical application of cytosine arabinoside in the treatment of varicella infections in children also suffering from leukemia, has been rewarded with considerable success. The recommended dose is 100 mg per square meter daily intravenously by rapid syringe injection. This was continued for seven days. Usually within 48-72 hours after starting therapy the old lesions dry up and no new crops are seen.

The occurrence of herpes simplex in prematures or newborn also requires rapid and intensive therapy. Moreover, the chronically ill child on immunosuppressive therapy with kidney, lung, or connective tissue disease, as well as those with hereditary or congenital defects in their immunity apparatus, are ready prey for infections, and viral infections, in these groups of highly susceptible children, are particularly devastating. Iododeoxyuridine, initially used in herpesvirus keratoconjunctivitis with considerable success, has been used in neonatal disseminated infections with some measure of success. Reports of its use in adults with herpesvirus hominis meningitis have also indicated variable results.

The use of an interferon inducer (polyinosinic-polycytidylic ribonucleic acid) in an infant with herpesvirus encephalitis was associated with rapid clinical improvement.

The development of severe virus infections in abnormally susceptible children should be rapidly evaluated and, if at all possible (weighing risk of disease against risk of treatment), treatment instituted.

J. J. QUILLIGAN, JR., M.D.

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Bellanti JA, Catalano LW, Chambers RW: Herpes simplex encephalitis: Virologic and serologic study of a patient treated with an interferon inducer. *J Pediat* 78:136-145, Jan 1971

Measles Vaccine Updated

Inactivated, "killed" measles vaccine is no longer available having proved to be unreliable and to provoke late hypersensitivity responses. Attenuated vaccines are available which cause only moderate febrile reactions after about eight days. Gamma globulin may be given coincidentally with the vaccine which reduces these reactions but also decreases the degree of immunity and is recommended only in conjunction with that virus grown on dog kidney.

Children should be vaccinated any time after one year of age, avoiding those with immune deficiencies, malignant disease, acute infections, etc. This is not 100 percent effective, but equals that of most other immunizations. The risk of late encephalitis from the vaccine is probably nonexistent, and children are protected from the severe acute infection and the devastating encephalitis.

During 1970 there was an increase of reported measles. This might have been prevented by more general use of vaccine but may also be due to the periodicity of measles epidemics and more conscientious reporting than formerly.

EDWARD B. SHAW, M.D.

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Report of the Committee on Infectious Diseases. American Academy of Pediatrics, 1970, pp 79-81

Synthesis of Human Growth Hormone

Dr. C. H. Li and his associates, who in 1956 first isolated and purified human pituitary growth hormone, and who in 1966 were able to determine its structure, announced in January 1971 that they had successfully synthesized the human growth hormone molecule. A complex peptide of a specific sequence of 188 amino acids with two disulfide bridges, it is the largest yet synthesized. The event is a major milestone in growth hormone research, although the amount produced was insufficient to adequately verify biologic activity. Among the possible investigative avenues opened by the discovery are those concerning the control of cellular growth, hormonal interrelationships in the regulation of metabolic processes and the control of lactation.

Of considerable interest is the possibility that human growth hormone may be synthesized in quantities sufficient for clinical use. To anticipate that this might be accomplished within the next decade is not unreasonably optimistic. On the other hand, a perhaps more realistic expectation is that the active "core" of human growth hormone will be found within the parent peptide and that this fragment may, in turn, be isolated in large quantities from the pituitaries of species other than man.

At present, some 20 percent of dwarfed children are found to have growth hormone deficiency and might benefit from human growth hormone administration. Such patients require approximately 1 mg per day of growth hormone obtained from cadaver pituitaries. However, the average adult human pituitary gland yields only 3 to 5 mg of the substance, and of the estimated 10,000 children with hypopituitarism, in this country alone, only about 6 percent are being so treated at this time.

ROBERT S. STEMPFL, JR., M.D.

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Important Advances in Phenylketonuria

The detection of phenylketonuria (PKU) by simple mass newborn screening methods discovered in the 1960's was a major breakthrough in the early diagnosis and treatment of metabolic biochemical genetic disorders. Most of the states in this country and many countries throughout the world now have mandatory screening. Early dietary treatment with careful monitoring of serum phenylalanine levels has proven effective in preventing mental retardation in affected children. A recent survey consisting of a questionnaire answered by 43 states revealed that 418 cases of PKU had been detected by newborn screening of 5.9 million infants, or an incidence of 1:14,100. (California's figures for the first four years of testing were 1:16,500.) Evidence from California and from the National Collaborative Study shows that

over 80 to 86 percent of those detected by newborn screening are on the low phenylalanine diet by 30 days of age. The intelligence quotient of these early-treated infants with PKU is usually in the normal range (85 to 100). The results of this experience have been documented and discussed in a growing literature on this condition.

GEORGE C. CUNNINGHAM, M.D.

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Phototherapy for the Jaundiced Infant

Phototherapy is effective in the treatment or prevention of hyperbilirubinemia, as noted previously in this Section (*Calif Med* 112:60, 1970). The blue portion of the spectrum (420 to 460 nm) is most active in the photo-oxidation of bilirubin, and in some studies blue lights have been clinically more effective than white lights. This difference may be particularly important in Negro infants. The photodecomposition products of bilirubin have been shown, in the human, to be rapidly excreted in the bile. In consequence, there is more assurance than formerly that the lower serum bilirubin levels do in fact suggest that the risk of neurologic change is decreased.

While blue light is more effective, its use makes nursing care more difficult, since all infants appear severely cyanotic when placed under blue light. Nursing personnel must be skilled in the detection of cardiac or pulmonary distress by signs other than cyanosis. The choice of blue or white light should probably be individualized, depending on the type of nursery. Shielding of the eyes is mandatory for infants receiving phototherapy.

In one study, reduced stature and small head size were noted in a two-year follow-up of premature infants treated with phototherapy. Differences were small but statistically significant. However, neurologic development was normal in these infants, and, in still other studies, no effect on growth was observed. While no major toxicity has been demonstrated, the possibility of unrecognized toxic effects still exists. Phototherapy should

be used primarily for the kinds of infants for whom it was previously recommended (Calif Med 112:60, 1970), and phototherapy should be discontinued as soon as it appears that a serious danger of hyperbilirubinemia has passed. Phototherapy should not be used for infants at no risk of neurotoxicity from bilirubin, and it is not an acceptable substitute in those situations for which exchange transfusion is clearly indicated. An occasional infant will require simple transfusion for anemia, even though the need for exchange transfusion is obviated by phototherapy.

BRUCE D. ACKERMAN, M.D.

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 Teberg A, Hodgman JE: Effect of phototherapy in low birth weight infants on growth and development at two years. Clin Res 19:224, 1971

Advances in Prenatal Detection Of Genetic Disease

Early amniocentesis combined with amniotic fluid cell culture and cytogenetic or biochemical investigations now makes possible the prenatal detection of several genetic disorders. These techniques offer parents at risk of having abnormal children the opportunity to undertake or continue pregnancies on the knowledge that the birth of affected children need not occur. The principal indications for the procedure are (1) risk of having a child with a chromosomal abnormality (parent carrying balanced translocation, previous child with Down's syndrome, mothers 40 years of age or older); (2) a woman carrying a serious X-linked disease (such as muscular dystrophy or hemophilia); and (3) parents who previously had a child with a serious inborn error of metabolism that can be detected in cultured cells. In each instance, the parents should receive complete genetic counseling before the amniocentesis, the procedure should be carried out by a competent obstetrician, and the cell cultures and analyses should be performed only in qualified laboratories.

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Simultaneous Use of Multiple Drugs

Recent advances have pointed out the value of the combined drug approach in many fairly ordinary clinical situations—for example, in patients presenting with illness involving more than one organ system, such as diabetes with infection and shock or coma, and congestive heart failure with pneumonia and thrombophlebitis. During his stay in the hospital a patient receives an average of ten drugs and sometimes as many as 30 to 35. The emerging recognition of important drug interactions is of critical importance to all physicians, especially practicing clinicians. The following reference should be required reading:

Azarnoff DL, Hurwitz A: Drug interactions. Pharmacology for Physicians 4:1-7, Feb 1970. (This is also reprinted in the publication, AMA Drug Evaluation 1971, first edition, pages xix-xxvii. Recently distributed to all members of the American Medical Association.)

RICHARD LEONARDS, M.D.

Rubella Vaccine

Three distinct, live attenuated rubella vaccines are now available for general use and over 20 million doses have been distributed. Although nine instances of neurological reactions have been *temporally associated* with the administration of rubella vaccines, none have definitely been ascribed to the vaccine to date. Aside from the above, the practicing physician should be aware of the following: (1) antibody responses occur in over 95 percent of recipients and the antibodies so engendered have not significantly declined over a four-year period, (2) although vaccine virus is shed in the pharynxes of recipients for as long as 40 days, it rarely spreads to susceptible contacts, (3) vaccine-induced antibodies protect against disease, (4) when challenged by natural rubella, subclinical reinfection of vaccinees occurs in approximately 50 percent of cases, (5) arthritis

follows immunization in about 50 percent of females more than 20 years of age and 5 to 12 percent of children and, (6) the embryopathic potential of the vaccine virus is not known. Because of this, the vaccine is contraindicated in pregnant women and vaccine administration to any post-pubertal females must be approached with caution. Indeed, vaccine has been inadvertently administered to over 100 pregnant females already. At present the U.S. Public Health Service has recommended that children in kindergarten and the early grades of elementary school deserve initial priority for vaccination. Because of reinfection, the unknown embryopathic potential and the reported temporally associated neurological reactions, a vaccine surveillance system must be included in any vaccine program.

BERNARD PORTNOY, M.D.

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Newborn Special Care

A major advance in health care during the past decade has been in newborn special care. Here all infants requiring special observation or special or intensive care—whether medical, surgical, diagnostic or therapeutic, infected or non-infected, full-term or premature, outborn or inborn—are admitted to one area specially equipped and staffed with specially trained personnel to provide to infants the attention required.

These units followed the demonstration that airborne transmission of bacteria in nurseries is inconsequential; direct transmission among infants by dirty hands from the infants' skins and cords acting as culture media are the mode and source of bacterial transfer. Antiseptic cord and

skin care of infants and hand washing by personnel prevent bacteria spread.

All hospitals delivering newborns require care areas near delivery rooms for acutely stressed infants. Definitive nursery care also must be provided in the same or in a different area. Extensive planning is needed, including provision of nurse and physician training programs, to help achieve this.

LOUIS GLUCK, M.D.

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Effects of Perinatal Nutrition on CNS Development and Function

Severe malnutrition during the first year of life will result in a reduced number of cells in the brain. This reduction is present within all regions studied, with the most pronounced effects in the cerebrum. Total cholesterol and phospholipid content are also reduced. These studies reinforce previous data in rats and pigs which demonstrated that cell division and myelination were curtailed in brain during neonatal malnutrition.

Evidence is also mounting in animals that severe maternal undernutrition will curtail cell division in the fetal brain. In the human several reports indicate that cell division is slowed down in placentas of malnourished mothers. Although more data are necessary, these studies raise serious doubts about the human fetus as a "parasite" and suggest that severe undernutrition during pregnancy may affect fetal growth and development.

MYRON WINICK, M.D.

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THE MISLEADING EEG SOON AFTER SEIZURE

"If you admit a child in febrile convulsions, status epilepticus, or prolonged focal fit, . . . your natural inclination is to order an EEG on him. But in a high percentage of cases, this will provide misleading information. The EEG records are often very slow, in a diffuse or focal way. Frequently you find misleading slow activity whereas if you wait a week—I'd say a week to ten days at least—you find a more representative kind of record. In other words, the first abnormality is simply a reflection of the insult to the brain of whatever happens during a severe seizure—whether it's anoxia, cerebral shock, or whatever you want to call it. The information is misleading. A week later you might find a petit mal kind of discharge or a focal kind of abnormality that's more important to you. If you don't wait, you wind up with EEG findings that look very bizarre. . . . Bearing this in mind will save you a lot of time and money."

—PATRICK F. BRAY, M.D., Salt Lake City
Extracted from *Audio-Digest Pediatrics*, Vol. 15, No. 18, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057.

On Cutting Costs in Health Care

IT IS NO NEWS that efforts to cut or even contain rising costs of health care have so far been singularly unsuccessful. Further, during the past year or so there appears to have been an unprecedented nationwide increase in the usage of health care services, a usage so great that it begins to threaten the financial solvency of health care programs of all kinds and even of the health insurance industry itself, with all that this implies. It is becoming imperative that something be done.

So far the approaches have been unbelievably simplistic and naive. Doctors have been blamed for increased utilization because after all it is they who order the services. Increased costs are also blamed upon the doctors who increased their fees, thus supposedly accounting for the increased costs, or upon alleged waste or inefficiency in the delivery of services. This has been great sport, but it has accomplished little because these are not the causes of the problem.

The true causes can be seen by simply looking at them. For one thing the dollar just isn't worth as much, and this alone makes the dollar costs in health care rise. But there are other causes. These may be grouped under progress in medical science, oversell of what medical science can do, and changing public attitudes. For the first, there is no doubt that much more can be done than before, that many more services can be useful for many more people, and that greater sophistication in health care generally results in greater costs. For the second, there is reason to believe that health maintenance has been greatly oversold in terms of what it can accomplish; certainly there is evidence that we are developing a drug-

oriented if not a drug-dependent culture and counter culture, and surely the decisions and awards of juries in malpractice action suggest that many persons are convinced that modern medical science is capable of more than it often is. And third, changing public attitudes have perhaps had the most important influence of all. High quality health care for all has been determined to be a right, and it is proving unexpectedly costly to make good on this commitment. Charity is giving way to dignity and equality not only for patients but for workers in the health care field, and this is another major factor in the rising costs. And most recently there has been an enormous and disproportionate increase in the number of hysterectomies, vasectomies and abortions which can be readily interpreted as reflecting the new social attitudes toward population control and unwanted children. In a real sense many of these are social services, yet their costs are ascribed to health care, and add significantly to the total.

Since the demands for health services are evidently unlimited and since what can be paid out for them is just as evidently limited, some action must be taken to bring what must be done into the range within which the people and the nation are willing and can afford to pay. Cutting physicians' fees or the allowable patient care services has so far been the main approach, but it has accomplished little and in the long run is likely to accomplish even less. Indeed it is about as simplistic and naive as is the accusation that all the trouble is due to the cupidity and inefficiency of physicians.

What, then, might be the approach? To start off, it might be acknowledged that adequate nutrition, satisfactory housing, sufficient economic maintenance and a certain level of education are more essential to achieving and maintaining a state of health than are any amount of federal, state or private health services. These costs should be separated out from the costs of health maintenance and health care, whether the patient is sick or well. True, there should be more em-

phasis on efficiency in health care delivery, but this emphasis should shift sharply from a frustrating and futile attempt simply to provide more of the same services to more people at the same or less cost. Rather it should be on reducing the number of unnecessary and unproductive services. Quite simply, those which are not worth their cost will have to be eliminated. This will require a challenge to many widely accepted but unproven assumptions with respect to the value of various products and services, and the circumstances of their use. Much more could be accomplished if the demand for unneeded services could be lessened without sacrifice of either the quantity or quality of what is truly necessary. For example, unnecessary services in enormous number are performed each day to relieve fears of heart disease, stroke or cancer—fears which we must admit have been publicly engendered by well-intentioned efforts to reduce disability and death from these conditions. And research should also be mentioned. For any disease the costs of care increase as progress is made against the disease until a major breakthrough occurs, following which the costs are sharply reduced. Tuberculosis, poliomyelitis and phenylketonuria may be cited as examples. However, the national policy of the moment is to curtail research and divert much of the available funds to patient care. Many questions could be asked as to whether this policy is wise or unwise in terms of present and future health care costs.

In conclusion it appears that the present problems are those of success—success in medical research, success in selling the public on the accomplishments of this research and the value of the health services which can now be made available, and success in moving toward the national goal of more health services for more people. It also appears that the present approach to cutting or containing costs in health care is not likely to accomplish much, and that little progress will be made until some widely accepted assumptions and attitudes with respect to the need for services are critically examined, the demand for unneeded services is substantially reduced, and much more attention is paid to the cost effectiveness of the services which are offered, with a substantial number of those which are not worth their cost being eliminated. The search for shortcuts and easy answers is likely to be both frustrating and in vain.

Phenylketonuria, the Inborn Errors of Metabolism, and Clinical Research—1971

On looking through my reprint collection in preparation for writing this editorial, it quickly became apparent that the file on phenylketonuria is one of the thickest for any single disease. Considering the relative rarity of the disorder (with an incidence of about 1 in 20,000 births) the recent vintage of the articles in the file, and the fact that my interest in phenylketonuria is really no greater than in any of a large number of genetic disorders, why would the folder be so thick? Why should so many research papers, review articles, editorials, and letters to the editor have appeared and continue to appear, so that even a reader with only a casual interest in the subject is inundated by them? In part the reason is historical. Although it was not the earliest inborn error described—Garrod's description of albinism, alkaptonuria, cystinuria and pentosuria antedate it by 30 years—it was the first metabolic cause of mental retardation to be genetically and biochemically defined, one of the first verified by enzyme studies, and, perhaps most importantly, one of the first for which a specific mode of therapy was developed. As a result, phenylketonuria became the prototype of the inherited enzyme defects and the subject of the considerable research activity which is represented in many publications. But, these "firsts" do not explain all of the interest in the disease, especially that in the last few years, and much of the explanation must be sought in the complexities of the disorder itself.

In the present issue of *CALIFORNIA MEDICINE*, Blaskovics and Nelson ably review many of the facets of phenylketonuria which are under active study and discussion. In broad terms these include the relationship of the mental retardation to the metabolic defect, the heterogeneity of conditions producing hyperphenylalaninemia, the effects of maternal phenylketonuria on fetal brain

development, the criteria for starting and stopping therapy, and the role of screening programs in the early detection of affected individuals. Each of these questions is, of course, discussed with reference to phenylketonuria, and there is no need to repeat the discussions here. However, the problems are certainly not unique to this disease, and their general significance is worthy of mention.

The inability to establish the mechanism by which absence of a specific enzyme ultimately results in impairment of neurological function, or of any other function for that matter, is as much the problem in maple syrup urine disease (branched-chain ketoacid decarboxylase deficiency) and the Lesch-Nyhan syndrome (hypoxanthine-guanine phosphoribosyltransferase deficiency) as it is in phenylketonuria. In fact, it seems to be the exception rather than the rule that knowledge of the enzyme defect has led to a clear understanding of the pathogenesis of an inherited metabolic disease. What was originally thought to be explainable in terms of absence of products or accumulation of precursors or their metabolites now requires consideration of potential mechanisms as diverse as allosteric changes in enzymes, the inhibition of cellular transport systems, interference with the synthesis of proteins and other macromolecules, and the disordered function of cellular organelles. The major problem is to sort out which effects are primary and causally related to the disease process and which are secondary and not of significance. This is a difficulty for investigations of affected individuals as well as for experimental approaches utilizing model systems. With regard to phenylketonuria itself, several proposals based on both *in vivo* and *in vitro* experimentation have been made for the site or sites at which phenylalanine and its metabolites interfere with brain development and function. To date, no agreement has been reached on which, if any, is the primary one.

Although it has long been recognized, the concept of the heterogeneity of genetic disorders has recently become quite popular, and numerous examples are now known. For the biochemical diseases, two principal types of heterogeneity can be considered: defects in different enzymes or metabolic processes producing the same disease or abnormality, and different defects in the same enzyme or system resulting in similar or dissimilar abnormalities. For example, several years ago it was recognized that cystinuria was of two types.

However, more recent investigations indicate that there are at least three genetically and physiologically distinct varieties, probably involving the same structural gene or genes. Likewise, two or more different mutations in the same structural gene have been identified for many other enzymes and proteins. To mention only a few, these include glucose-6-phosphate dehydrogenase (over 70 variants now known), hypoxanthine-guanine phosphoribosyltransferase (Lesch-Nyhan syndrome, familial hyperuricemia), galactose-1-phosphate-uridylyltransferase (classic galactosemia, Negro galactosemia, Duarte variant) and, of course, the many types of mutant hemoglobin chains. Depending on the precise nature of the mutation, the biochemical effect may range from complete loss of enzyme activity to only a slight change in electrophoretic mobility, and the clinical effects are equally diverse.

The other type of heterogeneity, that involving multiple causes for apparently the same clinical abnormality, has also been documented repeatedly. Again, to cite just a few examples, deficiencies of any of several enzymes in the glycolytic pathway give rise to nonspherocytic hemolytic anemias, defects in either the enzyme methylmalonyl-CoA isomerase or in the enzyme which converts vitamin B₁₂ to its 5'-deoxyadenosylcobalamin form result in methylmalonic aciduria, and absence of galactokinase or of galactose-1-PO₄-uridylyltransferase each results in the formation of cataracts when the patient is exposed to galactose. The situation with phenylketonuria, or more generally, with hyperphenylalaninemia, is far from being resolved. Hyperphenylalaninemia is quite heterogeneous clinically, and not all types are associated with retardation. It is not known whether all states of abnormal phenylalanine tolerance result from deficiencies, either transient or permanent, of phenylalanine hydroxylase. Likewise, it is not clear whether the heterogeneity results from a defect in the enzyme molecule itself, in one of the enzymes which carry out closely related reactions, or in some other enzymatic system. Even if only the persistent hyperphenylalaninemic states associated with high serum phenylalanine levels are considered, a one-for-one correspondence between the patient's ability to metabolize phenylalanine and the activity of the enzyme has not been established. This difficulty is related in part to the complicated nature of the enzyme reaction. It is aggravated by the scarcity of material with

which to work since, unfortunately, phenylalanine hydroxylase is found only in the liver and kidney, tissues obtainable only by biopsy or at surgical operation or postmortem.

The need for a correlation between enzyme activity and severity of the metabolic defect, and, more importantly, between each of these and the degree of intellectual impairment, is more than academic. Since testing of newborns is compulsory in many states and routinely performed in others, virtually every hyperphenylalaninemic infant is identified quite early. The most difficult decision confronting the physician who first evaluates such infants is to determine whether therapy should be instituted. If therapy were simple, inexpensive and completely innocuous, there would be little problem, but the therapy of phenylketonuria is none of these. Furthermore, it now seems probable that untreated hyperphenylalaninemia of a mild or moderate degree does not result in mental retardation and, conversely, that high and sustained levels of blood phenylalanine do. The difficulty is in deciding where to draw the line, in deciding which babies will become retarded if untreated and which will not. The development of better means for making this decision is of considerable importance.

Although better understanding of the enzymology involved is likely to contribute significantly, other factors will also require consideration. While variability of expression is taken as a matter of course in dominantly inherited disorders such as tuberous sclerosis, Marfan's syndrome and osteogenesis imperfecta, such variability is usually not expected in the recessively inherited metabolic defects. Nevertheless, several individuals with normal or near normal intelligence who apparently have "classical" phenylketonuria have been identified. Unfortunately, the reasons for the sparing of their intellectual functions have not, and therein may lie an important clue to solving the entire problem.

Among phenylketonuric persons with relatively normal intelligence have been several women who have given birth to retarded but non-phenylketonuric children. It is assumed that the cause of the retardation is the exposure of the developing fetus to high levels of phenylalanine or its metabolites during gestation. The implications of these findings are many. The most obvious involves the management of phenylketonuric women when they reach child-bearing age, particularly those

who have been successfully treated. It is now recommended that if such women undertake pregnancy (which many experts advise against) the mother's blood phenylalanine level be closely monitored and carefully controlled by diet. Another implication concerns the evaluation of children with manifestations of the maternal phenylketonuria syndrome of mental retardation, microcephaly and intrauterine growth retardation, a not very unusual combination of defects. Should evaluation of the mother for phenylketonuria be undertaken in all such cases? And might it not also be possible that other undetected metabolic abnormalities are present in the mother? And how far should one look for these? Answers to these questions are not as yet available, but they do require consideration.

On still another level, the broader issue of the long-term medical, genetic and social effects of treating any hereditary disorder can be raised. While it is not likely, it is certainly not impossible that the situation which has occurred with maternal phenylketonuria will occur in other entities. However, the more general concern is about the effect of allowing affected persons who previously did not survive or marry, to reproduce and thereby to transmit their "defective" genes to their children and increase the frequency of these genes in the population. While the rate of increase, measured in terms of generations, will be quite slow, an increase will occur and with it an increase in the incidence of homozygous affected persons requiring therapy. This problem has become of more immediate concern with the advent of the prenatal detection of genetic disorders, a method which is applicable to chromosomal defects, X-linked diseases, and a limited but increasing number of metabolic abnormalities—as yet not including, ironically, phenylketonuria itself. For the recessively inherited metabolic defects, the problem posed by prenatal diagnosis is similar to that of the treated homozygous patient. Through the termination of pregnancies in which the fetus is affected and thereby allowing its place to be taken by non-affected fetuses, two out of three of which will be heterozygous, a significant but still very small increase in gene frequency will occur. But, for the X-linked disorders and hereditary chromosomal abnormalities (balanced translocations), the effect on gene or carrier frequency will become apparent more quickly. Instead of a limitation of family size because of the high risk of hav-

ing an abnormal child (25 percent for female carriers of X-linked disorders and about the same for female d/c chromosome translocation carriers), the birth of children with a high chance of being carriers is favored. These children will, in turn, have the same problem as did their parents. Thus, both therapy and prenatal diagnosis will slowly lead to increase in what has been termed the "therapeutic load" of society. Although it is impossible to estimate the long-term significance of this "load," we must recognize that it exists.

In concluding this discussion, a few remarks about the relationship of phenylketonuria to clinical research in general are in order. In their review, Blaskovics and Nelson cite the differences of opinion which attend many aspects of the phenylketonuria problem, differences which are inevitable when all of the essential facts are not available. However, the degree of acrimony, both oral and written, which has attended these differences is not conveyed, and it is this intensity of feeling which is in some degree responsible for the mass of literature alluded to at the beginning of this editorial. An offensive posture in one quarter calls forth a defensive posture, followed by a counterattack, in another. More gets written to back up old positions than to develop new ones based on sound information. While the dispute in this instance involves phenylketonuria, its origins are not unique to this disease. Rather, they are much the same as for many other disputes, whether heated or dispassionate, which pervade clinical medicine. In general, the plot is as follows. A disease is studied, something of its origin and pathogenesis is learned, and a therapeutic approach is formulated. If the disease is one with very serious consequences, the therapy is first tried in a few far advanced cases. Gradually the applications become earlier, and individual trials are supplanted by larger series which apparently confirm the efficacy of the therapy. These series are rarely controlled, since it is felt that it would be improper to withhold a potentially beneficial treatment from someone in serious danger. But then questions arise. Is the therapy really effective, or is part of the good results a product of the "natural history" of the disease? Is the therapy actually safe, or is the morbidity or mortality greater than if it were not used at all? Are the criteria for deciding who should be treated sound, or are patients not likely to benefit or not requiring treatment being included?

The answers to many of these questions require controlled studies, the nature of the controls depending on the precise question being asked. But, unfortunately, the time for controlled studies is often past or, if not, such studies are difficult to institute.

This is not an unfamiliar story, if we think about such examples as the anticoagulant therapy of cerebrovascular accidents, the use of prophylactic antibiotics, or the treatment of rheumatoid arthritis. In the case of phenylketonuria, the therapy was reasonable, and limited studies indicated that it was effective. But the unexpected findings of large numbers of hyperphenylalaninemic children who did not become retarded, of persons with classical phenylketonuria who were not mentally deficient, and of untoward effects from overzealous treatment have raised all of the general questions cited above—and the time for carefully controlled studies, if it ever really existed, is certainly past. What is now required is careful assessment of the complex problems raised by the disease, reappraisal of what was done in the past, and a prospective approach to obtaining clear answers for the future. Only in this way will phenylketonuria ultimately fulfill its role as the prototype of the treatable inborn errors of metabolism and will the deluge of words, both written and spoken, finally be ended.

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Dealing in Futures

Part I—In Medicine And Health Care

Futures is a term used when a stock or commodity is bought or sold now for delivery at a future time. *Dealing in futures* is a phrase which can be used when money is being spent now to produce or buy a product which will be delivered and presumably used at some later time. It is suggested that in many aspects of medicine and health care this nation is investing as though only for today's

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market when actually it is dealing in futures. This can prove damaging if what will be needed in the future *must* be bought today so that it will be on hand at the time it will be needed.

Research and education are cases in point. These have to be bought and paid for now if their benefits are to be available for use in the future. The expectations and demands for what can be accomplished by medical research and medical education paid for now will be enormous in the decades just ahead. The needs for more knowledge and better medical services for this nation alone will be great, but one can anticipate even greater needs in the developing nations of the world as they seek and even demand parity in health care, as in many other things, where all on earth must learn to live together in order to survive. Yet obvious and well-documented as all these needs are, California and the country as a whole seem to be deliberately curtailing their investment in the research and education that it is so necessary to buy now in preparation for the predictable future.

It seems fairly obvious that these policies of short-sighted economic and political expediency, particularly in medicine and health care, will only serve to saddle those in the future with even more unsolved problems and even greater waste and expense. Democratic institutions, societies and especially governments have seldom been able to deal satisfactorily in futures, and this deficiency becomes increasingly significant and increasingly costly as the problems of population, environmental pollution and health and well-being inevitably assume more pressing social, economic and political importance throughout the nation and the world. Investment in medical research and education *now*, on the larger scale which is needed, would surely be a most economical kind of investment in the futures of health and health care. But this is not happening—not, at least, to the extent that it should. Some of the problems of dealing in futures in democratic societies and in democratic organizations will be discussed subsequently in these columns.

PREMATURE SYSTOLES: A WARNING

“Following a coronary occlusion a patient started to show single premature systoles, bigeminy, and then very frequent premature systoles, always from the same ventricular focus. Soon thereafter he went into ventricular tachycardia—obviously from the same ectopic focus (the shape of the QRS was the same). All of a sudden he went into ventricular fibrillation and died.

“This sequence of events can occur quite rapidly, and you might not have any more warning than the presence of premature ventricular systoles in excess of six per minute. Therefore you should start treating these premature systoles in the coronary patient as soon as possible. Bernard Lown demonstrated that if he could start dripping in either procainamide or lidocaine intravenously to patients as soon as he recognized these very frequent premature systoles he could prevent cardiac arrest. Killip doubted him very much but then ran through his series and confirmed the finding. When we combine their 300 cases of ‘garden-variety’ coronaries, we would anticipate 36 cardiac arrests according to our national statistics. But where they treated these patients prophylactically as soon as they recognized the frequent premature systoles or other arrhythmias, the number of cardiac arrests was only two in 300 cases. That’s an amazing decrease in the incidence of cardiac arrests.”

—ELIOT CORDAY, M.D., Los Angeles
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The Question:

SHALL ORGANIZED MEDICINE BE UNIFIED, or SEPARATE

At present, physicians in California who choose to join organized medicine do so through their county medical societies, and membership in the California Medical Association and the American Medical Association is then automatic. At the March meeting of the CMA House of Delegates, question was raised whether membership in CMA, and the AMA, or both should remain automatic.

The House requested an ad hoc committee to cause a "poll and its attendant statements to be developed by May 21 for copy distribution to component medical societies and printing in the CMA membership news media—with mailing of the official questionnaires to the society members on September 1, 1971." Members will be asked to express their opinions by ballot in September.

The Speaker of the House appointed an ad hoc committee of the House to conduct this informed opinion poll of the membership. The committee has met to set ground rules, prepare accurate pro and con statements and write the poll questions—in accord with the directions of the House action.

The Informed Membership Opinion Poll Committee, with the advice of Decision Making Information, Inc., an independent consultant, prepared statements regarding unified and separate membership in CMA and AMA from comments which were solicited from every county medical society. A statement by legal counsel for the California Medical Association on the structural relationship of AMA, CMA and component societies, and the statements on unified or separate membership prepared by the committee appear on the following two pages.

THE STRUCTURAL RELATIONSHIP OF AMA, CMA AND COMPONENT SOCIETIES

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Medicine's professional organizations are legally structured in three tiers—national, state and local. In the 19th century, the organizational structure was relatively loose, but at the end of the century, the present system emerged. Essentially, it centers at the state level.

AMA membership has not historically been the *basic* unit of membership, and in many states (including California) at various times it has been optional. On the other hand, the state association is the *basic* unit and, accordingly, state membership historically (in California since 1901) has been automatically linked with local membership.

The point is emphasized by the "Historical Notes" that have appeared in all modern printings of the Constitution and Bylaws of the California Medical Association. The Historical Notes first describe the situation in the 19th century when population was sparse and travel difficult. Then follows:

"With the reorganization of the state society, which followed on that of the American Medical Association in 1901, the picture changed.

"For in that year began the national association system made up of state society units, and these in turn composed of component county societies, only one such county unit being permitted for each county." (CMA Constitution and Bylaws, page 27, as adopted May 13, 1951—last full printing.)

The modern "system" may be outlined as follows:

(A) *American Medical Association*. As stated in the AMA Constitution (Article I), "It is a federation of its state associations." It is a federation made up of "recognized medical associations of states, commonwealths, territories . . . which are . . . federated to form the American Medical Association." (Article III.) Local or component societies are described as those county or district societies that are "chartered by the respective state associations." (Article IV.)

To the best of my knowledge, neither the Constitution nor the Bylaws of the AMA have ever *required* that all members of state associations be members of the AMA. There are provisions in the AMA Constitution and Bylaws for members of state associations to become regular members of the AMA (Constitution, Article V; Bylaws, Chapter I, Sec. 1). The Bylaws are couched in permissive language—for example, a state member "is eligible for Regular Membership" in the AMA if he is certified by the state association

and not disapproved by the Judicial Council (Bylaws, Chapter I, Sec. 1). Historically, some state associations have required their members to be AMA members and some have not, and some have changed policy from time to time (New York, for example).

Until recent years AMA dues were either nonexistent or nominal (nominal until 1911, nonexistent 1911 to 1949). From 1911 to 1950 the AMA financed itself almost completely through its various publications and did not need financial support from the practicing physician. The only charge made was \$10 per year to "Fellows," a special classification for physicians who did *not* belong to a constituent association. At the time the Fellowship classification was created, the House of Delegates noted that any physician joining a county medical society of a constituent state or territorial body "logically becomes a member of the AMA." AMA expenses increased about 1950 and dues payment on a modest scale commenced. Today the Congressional action taxing advertising income has made the AMA more than ever dependent on membership dues.

(B) *California Medical Association*. California Medical Association is *not* a federation. As stated in the "Historical Notes," it is the "unit" of membership. The CMA Constitution provides that CMA is an organization composed of "the component societies and their members . . ." and that component societies are those local organizations that are chartered by the CMA. (Constitution Article I, Sections 3-5.) Membership in the CMA and membership in a component society are totally linked throughout the CMA Constitution and Bylaws. In fact, the component societies are made the "sole judges" of the admissibility of an applicant for membership. (Bylaws Chapter II, Section 3.) Thus, when a component society admits a member, the admission is a dual one—to the component society and to its parent, the State Association. It is further specified that the Constitution and Bylaws of the component societies cannot in any way conflict or be inconsistent with the Constitution and Bylaws of the CMA (CMA Bylaws Chapter I, Section 1). The power to charter component societies is coupled with the power to revoke (Constitution, Article I, Section 5). California Medical Association, as currently structured, is the basic medical unit in California, functioning directly and through local societies chartered by it.

The identity of state and local membership is clearly spelled out in the "membership" chapter of the CMA Bylaws (Chapter 2). Not only are the component societies the sole judge of qualifications of an applicant both as to state and local membership, but also termination of component society membership automatically terminates state membership. In the CMA structure, local and state membership are synonymous.

STATEMENTS ON UNIFIED *vs.* SEPARATE CMA AND AMA MEMBERSHIP

In preparation for a poll of California Medical Association members as to whether membership in county medical societies shall be unified with or separate from CMA and AMA membership, the Informed Membership Opinion Poll Committee prepared the following statements of views on both sides of the question. Ballots and a questionnaire will be mailed September 1, 1971, to active and associate members of CMA, with a return deadline of October 15, 1971.

For Unified

CMA

The case for continuing the present system is based on the need for the strongest possible unified organization to speak for medicine in California, in the political, socio-economic, scientific and public arenas.

1. The problems we encounter in dealing with current issues such as governmental bureaucracy, legislation, changes in health care delivery, and third parties cannot be handled effectively by fragmented groups.

2. Benefits such as improving patient care, continuing education, malpractice legislation, socio-economic research, representation before governmental agencies, public information, and political action can be provided with vigorous and united membership support.

3. Active participation from within is far more effective in influencing appropriate change than "dropping out." Due to the complexity of problems facing medicine today, your voice and support are needed more than ever before.

Standing alone, the California physician is unable to deal with problems facing medicine today. Fragmentation guarantees ineffectiveness, while the potential of our unified voice is unlimited. The time for unity is now!

AMA

The current unified membership system in California links the individual physician into a close, strongly-knit unit and assures him of a forceful and effective voice at all levels.

1. While all CMA members may not agree with all policies and programs of the AMA, support of California's dynamic and responsive Delegation is necessary to promote a progressive national organization.

2. CMA representation in the AMA House of Delegates is based on the number of California AMA members. In order to strengthen our national posture, California needs a maximum number of members.

3. The full potential of benefits such as maintaining standards of medical education, evaluating and improving the hospital environment, representation before Federal agencies and political action are better derived by participation from a unified membership.

In short, simultaneous membership in state (CMA) and national (AMA) medical societies is essential to the unity and strength of the profession in this country, which is needed now more than ever before.

For Separate

CMA

The case for changing the present system is based on each physician having the right to make his own decisions voluntarily concerning the advantages and disadvantages of membership in each organization.

1. Elected representatives will be more responsive to the needs and desires of the membership if individual members have the opportunity to withdraw membership.

2. The organization would be strengthened by having as members only those who voluntarily choose to support its goals and objectives and the manner in which it speaks for the individual member.

3. Specialty groups offer comparable benefits to their members, such as malpractice coverage, disability and life insurance; therefore, CMA membership is unnecessary.

If the profession vigorously defends the principle of "freedom of choice" in health care, it should allow its individual members freedom of choice regarding membership.

AMA

Changing the present system would allow each physician the right to make his own decision voluntarily concerning the advantages and disadvantages of membership in the AMA.

1. A large majority of state medical associations currently offer this option, and to deny it is to deprive California physicians of their freedom to make a choice.

2. Some physicians advocating optional AMA membership contend that AMA is too liberal and its leaders do little towards preserving private practice. Others contend that AMA is too conservative and has failed to provide solutions to the surging tide of health problems.

3. If optional AMA membership is available, the AMA leadership would be more responsive to the wishes of California physicians.

AMA would be strengthened by having as members only those who voluntarily choose to support its goals and objectives and the manner in which it speaks for the individual member.

CASE REPORTS

Giant Cell Arteritis with Myositis and Myocarditis

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GIANT CELL ("temporal") arteritis, a disease classically affecting only medium-sized and large arteries, is often considered to be one of the "connective tissue diseases." Among the items of evidence supporting this conclusion is the occasional association of giant cell arteritis with the syndrome of polymyalgia rheumatica^{1,2} and a single documented case of associated myocarditis similar to that seen in other connective tissue diseases.³ Abnormal circulating antibodies may be present in patients with connective tissue diseases, and immunoglobulins are sometimes found within the specific connective tissue lesions.

An autopsy performed recently in Stanford University School of Medicine Hospital on the body of a patient with giant cell arteritis revealed both interstitial skeletal myositis and severe, clinically unsuspected myocarditis. Immunofluorescent examination failed to reveal immunoglobulin localization within the lesions.

Report of a Case

The patient, a 57-year-old white woman, was in good health until 15 months before admission

to hospital, she began to have severe back pain of obscure cause. Bi-temporal headaches and diffuse arterial occlusive disease of the lower extremities developed later. Biopsy of the right profunda femoris artery six months before the terminal admission to hospital showed typical giant cell arteritis. The patient was then referred to Stanford for evaluation, complaining of temporal headaches, occasional visual blurring, and ischemic symptoms in the legs. On physical examination she was observed to be well developed and normotensive (125/70 mm of mercury). Temporal and dorsalis pedis pulses could not be felt, femoral pulses were decidedly decreased and the carotid and radial pulses were normal. No ophthalmological abnormalities were noted.

Relevant laboratory findings included an erythrocyte sedimentation rate (Wintrobe) of 55 mm in the first hour; normal serum proteins except for raised Alpha 2 globulin (1.2 grams per 100 ml, making up 16.6 percent of total protein); normal immunoelectrophoresis; elevated serum complement (beta 1a/beta 1c) of 375 mg per 100 ml (normal 145 ± 22 mg); elevated fibrinogen of 1210 mg per 100 ml (normal 260-550 mg); negative direct Coombs test; negative latex fixation; negative lupus erythematosus cell preparation; negative anti-nuclear, anti-DNA, and anti-soluble nuclear fraction titers; and normal serum glutamic oxaloacetic transaminase and creatine phosphokinase. Skin tests with intermediate strength purified protein derivative and dermaphyton were negative.

An electrocardiogram showed Q waves in leads II, III, a VF and decreased voltage in the limb leads. Temporal artery biopsy showed an organized recanalized thrombus without definite evidence of giant-cell arteritis. On the basis of the clinical and laboratory findings and the previous femoral artery biopsy, the patient was thought to have generalized giant cell arteritis, and was started on 40 mg prednisone per day. This produced symptomatic improvement, and after one

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Submitted June 17, 1970.

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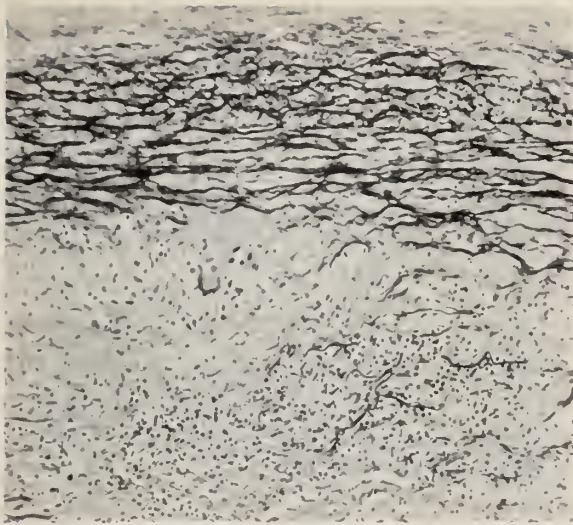


Figure 1.—Media of ascending aorta showing elastin breakdown and inflammation in the outer two-thirds of the media (Hematoxylin and eosin x 80).

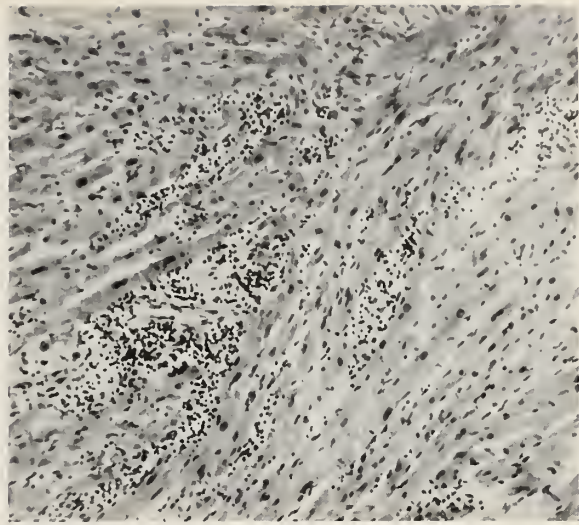


Figure 2.—Left ventricular myocardium (Hematoxylin and eosin x 80).

week the steroids were tapered and discontinued. Concomitantly the headaches increased and over a period of three days left hemiparesis and stupor developed. Lumbar puncture revealed grossly bloody cerebrospinal fluid. A right carotid arteriogram showed focal narrowing of the internal carotid and middle cerebral arteries, and swelling of the right cerebral hemisphere. The patient died a few hours later.

At autopsy there was diffuse thickening of the walls of the carotid, femoral, and subclavian arteries, and of the entire aorta. Histologically all these vessels showed the characteristic changes of giant cell arteritis, with medial necrosis, fragmentation of elastic fibers, and a heavy medial infiltrate of lymphocytes and histiocytes (Figure 1). Multinucleated giant cells were present, and were occasionally applied to fragmented elastic fibers. There was severe diffuse fibrous intimal thickening, and the fibrotic adventitia contained an infiltrate of lymphocytes, especially around the vasa vasorum. Histological sections of the superficial temporal region showed only very small arteries, with no evidence of inflammation.

The heart was grossly normal, weighing 250 grams, but histologic sections of the left ventricular myocardium showed numerous, diffusely scattered, poorly demarcated foci of interstitial inflammation, with extension into the adjacent epicardial adipose tissue in one place. These foci were composed of small lymphocytes, large his-

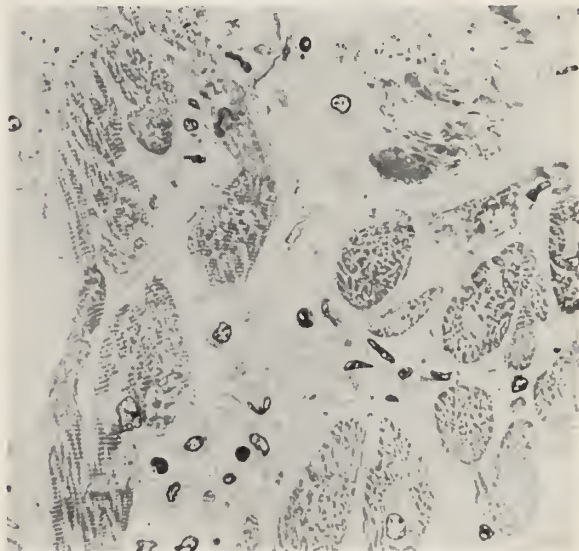


Figure 3.—Left ventricular myocardium, showing inflammatory infiltrate and degenerated muscle fiber at upper right. (1 micron section, Epon embedded—methylene blue x 320.)

tiocyte-like cells, and occasional polymorphonuclear leukocytes (Figures 2 and 3). Giant cells and lipofuscin-filled macrophages were absent. Occasional adjacent myocardial fibers were fragmented or necrotic. The foci of inflammation were apparently randomly distributed, although in places they abutted the endocardium or a small vein or a small artery. The intramyocardial vessels were normal. The epicardial coronary arteries were atherosclerotic, without evidence of giant cell arteritis. The epicardium and endocar-

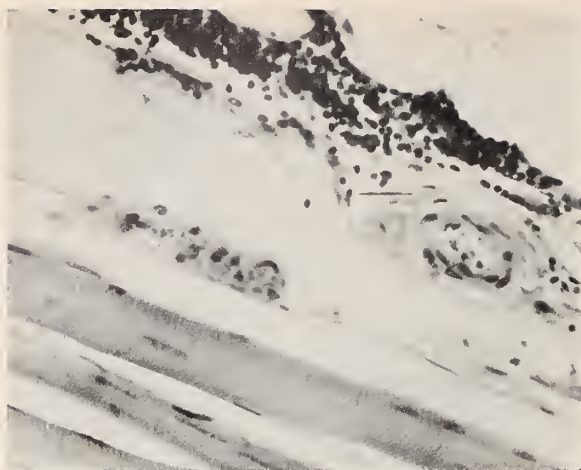


Figure 4.—Paravascular lymphocytic infiltration in the iliopsoas muscle (Hematoxylin and eosin $\times 320$).

dium were otherwise normal. Sections of the atria and the right ventricle did not show these changes. Electron microscopy of several areas of inflamed myocardium confirmed the light microscopic observations but did not provide evidence of virus infection.

Focal perivascular collections of lymphocytes were found in the interstitium of the iliopsoas muscle, the deltoid, and the extraocular muscles without associated changes in the muscle fibers (Figure 4).

The lungs and liver were congested but otherwise unremarkable. No abnormalities were seen in the skin, kidneys, thyroid gland, gastrointestinal tract or adrenal glands. The spleen, multiple lymph nodes and the Peyer's patches were unremarkable except for the absence of recognizable germinal centers. Plasma cells were present but were not numerous. The bone marrow was unremarkable. The thymus was not found.

Examination of the brain revealed a fresh 3 x 6 cm intracerebral hematoma in the right superior frontal gyrus with extension into the right lateral ventricle. Focal hemorrhages were present around small and medium-sized arteries adjacent to the hematoma but there was no definite histological evidence of vasculitis. Giant cell arteritis was present in both common carotid arteries with narrowing of the lumen on the right to about half its normal diameter. The vessels at the base of the brain were normal. The precise origin of the hemorrhage was not found. Sections of the eyes, central retinal arteries, brachial plexus and a pelvic nerve were normal.

Snap-frozen sections of aorta, carotid artery and heart were exposed to fluorescein-conjugated goat anti-serum to human IgG, IgM, and beta 1a/beta 1c (Hyland Laboratories, Los Angeles, California). Specificity of the anti-sera was verified by immunoelectrophoresis, and the titers of activity determined by the six-well Ouchterlony technique. We were unable by these methods to demonstrate the localization of IgG, IgM, or B1c/B1a in the lesions in the aorta, the carotid artery, or the heart.

In summary, this patient had giant cell arteritis of the aorta and its major branches, and died of intracerebral hemorrhage of unknown cause. Myocarditis and skeletal myositis were incidental findings at autopsy.

Discussion

Cerebral hemorrhage is distinctly unusual in giant cell arteritis and in normotensive patients in general. Unfortunately the cause of the hemorrhage could not be found in this patient, and there is therefore no definite evidence that it was related to arteritis.

The other findings of interest were the myocarditis and the interstitial skeletal myositis.

Diffuse interstitial myocarditis similar to that in this case has been seen in other connective tissue diseases, but has usually been less severe. Additional histologic features are often seen. Interstitial fibrinoid deposition, intramyocardial vasculitis involving small arteries and veins, or associated Libman-Sacks endocarditis may occur in systemic lupus erythematosus.⁴ The myocarditis of rheumatoid arthritis is frequently localized to the left ventricle near the mitral ring, and focal lesions are sometimes related to small vessels. Rheumatoid granulomata may be found in the aortic and mitral valves, or in the myocardium. Active or healed arteritis may also be seen.^{5,6} Diffuse nonspecific myocarditis is common in acute rheumatic fever; the additional findings of Aschoff bodies is diagnostic. The myocardial lesions which may occur rarely in dermatomyositis resemble the skeletal muscle lesions with focal degeneration of myofibers and a scanty inflammatory infiltrate.⁷ Scattered myocardial scars may be seen in scleroderma but active myocarditis has not been described.⁸ The majority of the myocardial lesions of polyarteritis nodosa are secondary to arteritis of the coronary

arteries, but nonspecific myocarditis has been observed.⁹

In the only other documented case of myocarditis in giant cell arteritis the histological appearance was somewhat different.³ In addition to interstitial myocarditis resembling that seen in the present case, there were focal granulomatous infiltrates with central fibrinoid necrosis, often around small interstitial vessels.

Many infectious agents may cause interstitial myocarditis similar to that seen in the case here presented. Bacterial and parasitic myocarditis can be ruled out on histologic grounds, but serologic studies to exclude viral myocarditis were not done because the myocarditis was completely unsuspected at autopsy.

The failure to demonstrate viral particles electron microscopically suggests, but does not prove, that this is not viral myocarditis.

Immunofluorescent studies of the connective tissue diseases have shown that immunoglobulins may be present in the heart in rheumatic heart disease,¹⁰ in the synovium and subcutaneous nodules in rheumatoid arthritis,¹¹ in the kidney in systemic lupus erythematosus,¹² and in the blood vessels in polyarteritis nodosa.¹³ Immunofluorescent examination of the blood vessels in giant cell arteritis and of the cardiac lesions in the connective tissue diseases—with the exception of rheumatic heart disease and acute rheumatic fever—have not been reported to our knowledge.

The failure to find immunoglobulins within the myocardial and vascular lesions in the present case suggests that if an immunologic reaction is responsible for the lesions, it is not associated with accumulation of IgG or IgM at the site.

The syndrome of "polymyalgia rheumatica" frequently occurs in patients with previously unsuspected giant cell arteritis.^{1,2} Muscle biopsy is usually normal,^{2,14} but focal interstitial lymphocytic infiltrates have occasionally been seen.^{15,16} In the present case the lymphocytic infiltrates were adjacent to very small arteries which were microscopically normal. Although the lesions were widespread in the muscles examined, they were not numerous, and could easily have been missed on routine muscle biopsy. Perhaps post-mortem examination of large pieces of skeletal muscle in polymyalgia rheumatica associated with giant cell arteritis would reveal focal interstitial myositis more frequently.

Giant cell "temporal" arteritis is already recog-

nized as an inflammatory disease which may affect not only the temporal arteries but all large and medium-sized arteries. It is hoped that this report will stimulate more detailed study of myocardium and voluntary muscles in cases of giant-cell arteritis coming to autopsy in the future, so that it may be established whether the myocarditis and myositis recorded here also form part of the spectrum of this disease. Such observations might lend support to the concept of giant-cell arteritis as one of the group of "connective tissue diseases."

Summary

The history and autopsy findings are presented in a case of giant cell arteritis, myositis, and myocarditis. It is suggested that such evidence of extra-arterial inflammation might lend support to the view that giant cell arteritis is related to the "connective tissue diseases."

Acknowledgements

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New Methods of Psychiatric Treatment

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■ *There have recently been many innovations in the field of psychiatric therapy. Many of the new techniques challenge some of the underlying assumptions of conventional psychiatry. Some methods, such as reality therapy and behavior therapy, attack the symptom directly, rather than assuming there is an underlying disorder which must be treated. Another, crisis therapy, stresses brief intervention aimed at rapidly reestablishing previous levels of function, with relatively little concern for insight into developmental causes. Or, as in family therapy, the pattern of family interaction rather than the individual may be the primary object of study and treatment. Each of the new methods of treatment has certain advantages as well as disadvantages. They have stimulated psychiatry to explore innovative methods and should make it possible eventually to incorporate in the treatment of each individual those techniques which will most effectively meet his needs.*

DURING THE PAST 15 YEARS, many new techniques of psychiatric therapy have emerged. While many of them hold promise for increasing the effectiveness of psychiatric treatment, there is at present little in the way of objective data with which they can be validated. As a result, a physician referring patients for psychiatric consultation may receive suggestions for a bewildering variety of types of treatment.

Suppose a 35-year-old housewife, mother of two, with depressed mood, irritability, insomnia,

increased alcohol intake and tension headaches is referred. Will the recommended treatment be intensive long-term individual psychotherapy, given at several sessions a week, or will she be seen for a limited number of visits in order to deal with only those factors which can most quickly help her regain her former level of functioning—crisis therapy? Will the focus be upon attaining a dynamic understanding of the psychological experiences which have caused and sustained her maladaptive behavior, or will it be upon clarifying and giving her an opportunity to change selfish or irresponsible behavior which decreases her own self-esteem—reality therapy? Will she be treated conjointly with her husband,

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or will the children be included, or even the three generational family—family therapy? Or will she be treated in a group with other adults, perhaps in one emphasizing awareness of an expression of feelings about the self and others—encounter group? Or will she be treated with aversive conditioning of her symptom of alcohol abuse—behavior therapy—or by discussion of the basic problems of what it is to be human, in order to help her find meaning in her life—existential therapy? Or will she be given disulfiram to control her drinking, or tranquilizers for her anxiety and tension headaches, or antidepressants for her depression?

For many years, the focus in psychotherapy has been upon the individual. The intrapsychic processes, attitudes, and assumptions which underlie the individual's behavior and relationships are the object of study. While current behavior, particularly as it influences the doctor-patient relationships, is explored, much emphasis is placed upon understanding the antecedent origins of significant behavioral traits.

It is assumed that the early feelings and attitudes which the child develops toward his parents and siblings remain relatively fixed, and form the basic pattern for subsequent relationships. Psychotherapy must deal with this basic pattern of attitudes and feelings; it is directed toward this permanent nucleus of the personality. It is assumed that insight into the developmental causes and current manifestations of inappropriate behavior leads to more satisfactory ways of functioning. Some of the newer therapies challenge in one way or another these underlying assumptions. In what follows, these newer techniques will be contrasted with the more conventional dynamic psychotherapy.

Reality Therapy¹

One of the underlying assumptions of reality therapy is that people do not act irresponsibly because they are "ill," but that they are "ill" because they act irresponsibly. Herein lies a basic theoretical difference between reality therapy and conventional psychiatry. Conventional psychodynamics assumes that very often individuals fail to achieve satisfaction in their relationships with others because of certain basic fears, such as of being rejected, humiliated, or exploited by others. As a result, they have excessively high

expectations of themselves, which must inevitably fail, with resulting feelings of inadequacy, and production of various defensive maneuvers for obtaining substitute satisfactions. Adherents of reality therapy would say that this is putting the cart before the horse—that the individual is not ill because he sets unnecessarily high standards for himself, but because he has not maintained a satisfactory standard of behavior. He will suffer from low self-esteem for realistic reasons because his behavior really is not worthwhile. Thus, the patient must learn to use new, responsible patterns of behavior, because so long as he continues to behave in an irresponsible way, he will be unable to fulfill a basic need to feel worthwhile.

A further basic tenet of reality therapy, which sharply differentiates it from more common contemporary psychotherapy, is the assumption that changing behavior is entirely a part of one's present life, with little relationship to the past. However deprived an individual's past life may have been, or how it may have affected him, it is generally ignored as irrelevant to the attempt to help him to fulfill his needs at the present time.

The original determinants of "sick" or irresponsible behavior are considered to reside in interaction with parents who were unable to teach the child to behave responsibly by setting appropriate limits to his behavior, often because of inability to tolerate the child's anger. During treatment, the therapist must always take the responsible rather than the expedient course in his relationship with the patient. He must withstand demands for sympathy, support, unnecessary medication, and the like, in spite of the patient's suffering or angry demands. Rather than remaining aloof, the therapist becomes emotionally involved with the patient, who must feel that here is someone who cares about him. The therapist accepts the patient as he is at first, without becoming frightened or rebuffed by his behavior. Developing out of this involvement, the therapist begins to insist that the patient face the reality of his behavior. A manifestation of the therapist's concern for the patient is his insistence that the patient face the truth that he is responsible for his own behavior. The patient's attitudes are of only secondary concern; he must begin to behave in more re-

sponsible ways. Waiting for attitudes to change is believed to stall therapy, whereas behaving in a different manner can lead to changes in attitude.

Although it is recognized that the past has certainly contributed to what the patient is now, the past cannot be changed. Understanding why a certain piece of behavior has developed may be interesting, but will not in itself lead to change. In conventional psychotherapy, it is recognized that a patient who has achieved some degree of insight, but without change in symptomatic behavior, may still demand of the therapist, "What are you going to do about it." Here the patient must come to recognize that only he can decide what to do with his insight. In reality therapy, it is made explicit from the outset that the responsibility for change resides in the patient. The reality therapist attempts to help the patient see the way his irresponsible behavior contributes to failure to satisfy his basic needs, and to make him more fully aware of the reality of and consequences of his behavior. The patient must understand that change in his responsibility. The therapist then helps him find new ways of behavior which conform to the patient's standards and which are consistent with the world as it really is.

Behavior Therapy^{2,3}

Within the past ten years a type of therapy has emerged which is aimed at controlling symptoms of emotional disorder by the application of principles of learning theory which have been developed in experimental psychology laboratories. Maladaptive behavior is conceived of as being learned and maintained in much the same way as adaptive behavioral traits. Psychiatric syndromes are viewed as constellations of learned faulty habits. Emphasis is given to identification and modification of those observable conditions which influence the behavior to be changed. In many ways, this approach would appear to be antithetic to that of conventional dynamic psychiatry. In the latter it is assumed that symptoms are outward manifestations of some underlying disorder. Symptomatic relief is achieved through altering the underlying disorder, as is the case with the medical model. Hence, an irrational phobic fear would be approached therapeutically by attempting to understand the underlying emotional conflict which

was displaced into the overt symptom. The behavior therapist, on the other hand, would view the symptom as the disorder, and would aim at symptomatic control through altering the conditions which elicit and maintain (or reinforce) the behavior. While conventional psychotherapy directs its efforts toward modifying antecedent thoughts and feelings upon which the behavior depends, helping the patient to understand the situation in a new way which will lead to behavioral change, behavior therapy focuses directly on the overt behavior itself. The therapeutic process in general consists of specifying the behavior which is to be modified, trying to determine the conditions which produce the behavior and which result in its persistence, and then in arranging a schedule of retraining to which the behavior is systematically subjected.

Learning theory is a description of the processes which change the probability that a given response will be elicited by a given stimulus. Some learning can best be described in terms of Pavlov's conditioning theory. A neutral stimulus, when paired with a stimulus which already has the power to elicit a certain response, will after a certain number of trials acquire the ability to produce the response. The classical example of this is Pavlov's dog, salivating at the ring of a bell which has previously been paired with a food stimulus. Other learning is best explained by a second theory, termed *operant conditioning*, which is based upon the manner in which a given response is maintained or inhibited by the environmental response which it elicits. An example of this would be the way in which the type of parental response can either extinguish or reinforce a child's temper tantrums or eating problems.

Behavior therapy techniques may be based upon either of these theories. One group of deconditioning procedures is based upon modification of the relationship between the behavior and the situation in which it is elicited. An example of this would be a desensitization technique used to modify specific fears or phobic reactions. Thus, an individual with a phobic disorder would be repeatedly exposed to gradually increasing levels of the feared stimulus until it would no longer elicit the previous exaggerated

response. A related technique, reciprocal inhibition, is based upon the fact that certain response patterns are mutually incompatible. The method of reciprocal inhibition and desensitization combines these techniques. A list is compiled of the situations which elicit the fear response, ranked in ascending order of intensity. Then, after the patient has been trained in relaxation procedures through instruction or hypnosis, he is asked to visualize or imagine the fear-inducing situations while he is relaxed, beginning with the weakest. In these circumstances, relaxation may inhibit and replace the fear. This is often generalized to the real life situation. Another technique, *conditioned avoidance*, is based on pairing an unpleasant, aversive stimulus with the unwanted behavior. For example, an electric shock may be paired with exposure to a fetish object, or an emetic drug may be given simultaneously with alcohol ingestion. Under these conditions, with an aversive stimulus being repeatedly associated with the stimulus which has elicited the unwanted behavior, a conditioned aversion develops to the formerly attractive stimulus and the behavior is extinguished.

A second set of techniques, based on operant conditioning theory, aims at modification of the relationship between the unwanted response and its consequences. An example of this is the use of positive reinforcement, in which a desired behavior is systematically followed by a satisfying consequence. Thus for a patient with anorexia nervosa, visits and privileges might be contingent upon the desired eating behavior. This technique has been used in eliciting more socially effective behavior in hospitalized schizophrenic patients and in autistic children. A related technique, *aversive conditioning*, decreases the likelihood that unwanted behavior will occur by exposing the individual to unrewarding consequences whenever such behavior occurs. An early example of this was the treatment of enuresis by arranging conditions so that wetting the bed caused a bell to ring which awakened the child.

Behavior therapy would seem to have its greatest utility in disorders manifest by specific overt behaviors such as excessive fears and phobias, abnormal habit patterns such as tics

and stuttering, certain kinds of repetitive compulsive behavior, alcoholism, and some sexual perversions. It has had a beneficial effect on conventional psychiatry by compelling it to examine its underlying assumptions and to frame its theories of psychopathology and treatment in more explicit, verifiable ways. Despite its success in dealing with certain symptomatic behaviors, it is still too early to evaluate the effectiveness of behavior therapy in dealing with the more complex, entrenched psychiatric syndromes.

Existential Therapy^{4,5}

Traditional psychotherapy has considered its domain to be the treatment of mental illness. Its concern has been with symptoms which are ego-alien. The basic goal has not been to give meaning to a patient's life or to provide him with some philosophy by which he might live. Nevertheless, psychiatry has necessarily attempted to deal with pervasive characterological states manifest by feelings of alienation, futility and meaninglessness. While conventional psychiatry would view such subjective feelings as being a result of neurotic defensiveness in relationships with others, existential psychiatrists view them as a consequence of human existence. European psychiatrists such as Jaspers and Binswanger have applied the concepts of the existential philosophers to psychiatry. Man is the only animal capable of wondering about the meaning of his life, or of knowing that inevitably he will die. He may develop religious or mystical concepts of the meaning of life or can experience the anxiety of meaninglessness or the absurdity of fate when his beliefs are threatened. To some existential philosophers and psychiatrists, the question, "Is life worth living at all?" is not necessarily a manifestation of psychopathology but is an expected consequence of man's existence.

Existential psychology centers upon the existing person particularly as he is in the process of emerging and "becoming." It does not reject attempts to understand man in terms of his basic drives, reflexes and so forth, but denies that a person can ever be completely understood in those terms. A human being has the capacity

for self awareness. This gives him the freedom to make choices, but also imposes the necessity to make choices. Existing and "becoming"—the process of self realization—depend upon the individual's courage to make choices, the "courage to be." This inevitably involves risks, for choices must be made, even though one can never have absolute certainty. Lack of the courage to be may cause the individual to hide from the reality of his existence, and relate to others in anxiety-driven, inauthentic, defensive ways which give rise to a feeling of emptiness.

Existentialism has not introduced new techniques into psychotherapy, but has emphasized a point of view. Many of its concepts, if not its terminology, are being incorporated into current psychotherapy. In therapy the patient is helped to realize that protests and resentments against past injustices or fate cannot alter them, but that he has in him the potential of self actualization and authentic relatedness which will help him to transcend the fear of nothingness. While for some existential psychiatrists, concerns about the meaninglessness or absurdity of life are legitimate, conventional psychiatry tends to view such feelings as psychopathological. In practice, it is often seen that such existential concerns are diminished, even though not attacked directly, when an individual's capacities for mature, loving relationships with others is improved.

Family Therapy^{6,7}

Family therapy is a method of intervention that studies and influences the family as a functioning unit. The individual is not considered in isolation but in the matrix of his significant human relationships. Intrapsychic processes are not of primary concern; family dynamics, the role of family members and their communication patterns are the objects of study.

As one corollary of these assumptions, the family member who is identified as "ill" is considered to be only an outward manifestation of disturbed family interaction. He may be a scapegoat whose "illness" justifies on-going pathologic family functioning. It may be discovered that the identified patient is less disturbed than some other family member, with this becoming particularly apparent when a change in the patient's behavior results in a decompensation of another family member.

The family therapist works with the family as a group. All family members are present at each session, and this may be even extended to include three family generations. The concern is not with the disturbance of individual family members, but with the functioning of the family unit. Since family experiences are assumed to have played a paramount role in influencing the healthy or unhealthy mental development of its members, it is assumed that the family group will be most potent in promoting recovery. A basic belief is that individual and family interests are not contradictory, but that in the long view, the needs of family members are complementary, and that the individual is best served when the needs of the whole family are considered.

The family therapist functions as a catalytic agent to elicit and clarify basic areas of conflict within the family, and to elaborate and explore their expression and consequences for all family members. He attempts to clarify the real content of conflicts, while confronting family members with inappropriate displacement of the conflict. He attempts to neutralize the scapegoating of individual family members which is often involved in displacement. Concealed or disguised areas of interpersonal conflict are brought into the open so that they can be dealt with realistically. The family therapist also actively intervenes in suggesting improved, alternate ways of family functioning and in attempting to exert a positive influence on family identity and values.

In theory all classes of psychiatric and psychosocial disorder may be treated by family therapy. The technique appears particularly useful where the disturbance of a family member is having repercussions on the adjustment of the family as a whole, and in which it appears that distorted but persisting attitudes of one or more family members has a persisting pathological effect.

Crisis Therapy⁸

Crisis therapy is a method of psychiatric treatment based on a relatively new conceptual model which is becoming increasingly available in many community clinics faced with the need to provide services to many patients. It should be noted, however, that its proponents do not see it as a second-best alternative to long-term therapy or treatment in hospital, but as a brief technique which in certain situations may be

equally effective in restoring previous levels of functioning.

Crisis theory had its origins in the work of Lindemann,⁹ who observed bereavement reactions in families of victims of Boston's Coconut Grove nightclub fire. Observations on the reactions to crisis situations have been supplemented by observation of military combat casualties and survivors of tornadoes and other disasters. Crisis theory conceives of individuals as maintaining a state of relative emotional equilibrium through the use of habitual coping techniques to deal with intercurrent stress. However, when a hazard is so severe or novel that customary problem-solving mechanisms are unsuitable, a crisis situation is produced. This results in a state of discomfort or tension which may temporarily cause behavioral immobilization or disorganization. A key implication of this theory is that during the period of crisis the individual is ripe for change in a relatively short time. If his emergency coping techniques are inadequate, he may re-integrate at a lower level of functioning; however, during the period of disequilibrium there is a potential for learning improved coping techniques which may result in the return to a higher level of functioning and an enduring improvement.

The technique of crisis therapy stresses primary attention to the events which have precipitated the crisis, rather than to earlier developmental influences which may have caused personal vulnerability. The therapist takes an active part in helping the patient gain an objective understanding of his present circumstances, and of his feelings about the issues with which he must deal. He encourages him in the use of his customary coping mechanisms or of alternate adaptive techniques. While the therapist takes an active role in this regard, the patient's responsibility for his own behavior is encouraged. Although advice is given in terms of alternatives which should be considered, the responsibility of the patient for decisions affecting his life is not undermined.

Indications for crisis therapy include emotional disturbances occasioned by such events as death of significant family members or friends, job loss or change, quarrels or separations from loved ones, moves, serious illness in oneself or a family

member, or entering a new stage of life such as the menopausal period. As part of a current trend to treat larger numbers of patients in the community, in earlier stages of their disturbance and without separation from family or occupation or customary activities, crisis therapy has a significant place. As a technique with promise of meeting some of the mental health needs of the community, it warrants further development and investigation.

Encounter Groups¹⁰

Although not really a form of psychiatric therapy, encounter groups warrant consideration here because they overlap the field of group psychotherapy. They undoubtedly attract some people with symptoms which would otherwise lead them to some form of mental health care. These groups, variously known as encounter groups, T-groups, sensitivity training or human potential groups, are not basically oriented toward treatment of symptomatic or ill individuals, but, depending upon the orientation of the particular segment of the encounter group movement, are variously aimed at (a) increasing trust, candor, and personal awareness in interpersonal behavior, (b) teaching the principles of small group process, or (c) achieving a transcendental personal experience. In some cases, well publicized techniques such as nude groups, or marathon groups of extended duration are used. Most such groups aim at providing an intensive group experience by encouraging open and candid expression of personal feelings and interpersonal confrontation.

There has been a phenomenal growth in the encounter group movement in the United States, and particularly in California. This perhaps reflects the diminishing importance of other groups in our culture which traditionally have provided for basic needs of interpersonal support and intimacy. It has been estimated that 50,000 individuals have participated in at least one of the programs of Esalen, at Big Sur, California, and there are approximately 75 other similar though smaller centers across the country. Although many groups are sponsored by universities or professional organizations, some have no institutional affiliation and are conducted by group leaders with no formal training in the behavioral sciences or mental health fields.

There is little doubt that participants in encounter groups may undergo a significant emotional experience. Such groups can provide a type of self-awareness which promotes personal growth and enhances interpersonal relationships. However, psychiatric casualties from encounter groups also occur. This is not surprising, since the group experience can be profound, and some group leaders, untrained in the mental health field, are unable to recognize overt psychiatric disturbance. In some groups, brutally candid interpersonal confrontations have been known to precipitate overt psychotic reactions. Presumably these occurred in persons who had been maintaining a borderline adjustment. Rather than overt psychiatric disturbance, some persons may gain a biased, overly simplistic, negative type of "insight" which, rather than enhancing interpersonal skills, results in further erosion of self esteem. One highly reputable organization, the National Training Laboratory at Bethel, Maine, in a follow-up study found that the psychiatric casualty rate, as measured by admittance to hospital, overt psychosis or a need for psychiatric attention, was about 0.5 percent of the participants.

Encounter groups are inherently neither good nor bad. They have potential for constructive change, and their techniques have stimulated new methods and techniques in the field of group therapy. However, conducted by untrained persons with no experience in the professional mental health disciplines, they may result in adverse effects. They have been called "group therapy for normals"; they are not appropriate for the treatment of persons with severe emotional disorder.

Lithium in the Treatment of Manic States^{11,12}

Drug therapy of psychiatric disorders has been well summarized elsewhere,¹³ and will not be reviewed here. However, the use of lithium carbonate in the treatment of manic-depressive disorders warrants comment because the drug has only recently been approved by the FDA for general, non-investigational use. For many years it has been clear that lithium salts can effectively control many cases of manic disorder. It has been used as an investigational drug, requiring FDA approval, many places in the United States,

but its approval for general use has been delayed because of the hazards associated with its use. It has a very narrow therapeutic range, with the effective level being only slightly lower than the level which causes serious toxic symptoms.

It is now widely accepted that manic episodes which are part of a recurrent manic-depressive disorder often respond within a few days to effective doses of lithium. There is also considerable evidence that when used at a lower maintenance dose, it can effectively prevent recurrent manic attacks. However, with intervals as long as a year or more between attacks, lithium maintenance may not be justifiable. For use in individual attacks, the choice of lithium rather than phenothiazines must be weighed against the risk involved. Contraindications include renal and cardiac disease.

Lithium is now available by prescription as lithium carbonate in 300 mgm capsules. The effective blood level for control of hypomanic symptoms is approximately 1.0 to 1.5 mEq per liter. Initial dosage is between 900 and 1800 mg a day until an effective blood level is reached. This should be reached within a few days, then maintained for a trial period of ten days. During this time, serum lithium determinations should be made every 48 hours, with the patient being observed closely during this time for complications. These include nausea and vomiting, tremor and ataxia. At the beginning of treatment mild gastrointestinal symptoms, hypotension, diarrhea and fine tremors of the fingers are often seen. If serum determinations show lithium levels above 2 mEq per liter at any time, then the dose should be reduced and extra fluid given. At levels above 3 mEq per liter, arrhythmias, circulatory collapse and coma may ensue. This demands immediate discontinuance of the medication, and increased fluid intake with parenteral fluids. During the first ten days of treatment, blood pressure and pulse should be taken before each dose is given, and adequate fluid intake of 1 to 2 liters per day should be insured. After adequate symptom relief is achieved, then a maintenance level of approximately 0.5 to 1 mEq per liter is appropriate. During this time serum lithium determinations should be made twice a week, which may be gradually extended to one time monthly.

Although treatment with lithium salts is potentially hazardous, it can be, if care is exercised, a

safe and effective treatment. It can be uniquely effective in some patients in the control of otherwise disabling recurrent manic attacks.

Conclusion

At the present stage of development, no method of psychotherapy can be considered comprehensive and total. Each has certain strengths along with certain limitations. Although the most common psycho-social treatment now practiced is a dynamic psychotherapy, based on analytic principles, which is months or years in duration, it is likely that it will become increasingly infused with some of the newer techniques. Unfortunately, at this time, the selection of some of these therapies appears to be based more upon the experience and enthusiasm of the therapist than upon realistic assessment of the needs of the individual patient. With more experience, and with more rigorous assessment of the outcome of various types of therapy, it is to be hoped that it will become increasingly possible to assign a patient

to the therapy incorporating the techniques which will most effectively and economically meet his needs.

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"ADDICTION TO NOSE DROPS"

"One of the most aggravating problems with the nose is topical rhinitis medicamentosa, caused by the over-use of nose drops. . . . A rebound phenomenon and eventually a full addicting reaction can result if the drops are used long enough.

"My advice is to get the patient off nose drops, and don't prescribe them for a chronic condition. A general rule we have is: Don't prescribe a nose drop for longer than five to seven days. . . . If the patient would only read the rules for nose drops and nasal sprays and follow them, he wouldn't get into trouble; but he doesn't. A lot of nose drops are now available across the counter. The patient buys them and then regulates the dose himself, increasing the amount as the effectiveness decreases. Each time he uses them the period of therapeutic effect is shorter, the rebound is harder. Nose drops meet every quality of an addicting drug.

"There's a very easy way to get most patients off nose drops if you have their cooperation and they are physically otherwise able to do it. That is to stop the nose drops abruptly and put them on a dose card use of any of a half dozen steroids, including Medrol® or Aristocort.® Any of this group carried over a five- to seven-day period of gradually withdrawing doses will break the rebound phenomenon and clear the nose. Of course, when the nose is cleared, then you have to get on the original problem and find out why it was bad enough for the patient to start on the nose drops in the first place."

—HUESTON C. KING, M.D., Miami
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LETTERS *to the Editor*

"Pharmacist and the Physician"

To the Editor: The recent article, "The Pharmacist and the Physician," by J. E. Goyan which appeared in CALIFORNIA MEDICINE, May 1971, page 95, is an interesting array of information regarding one of the most vexing problems in American medicine, namely, the widespread use of drugs by physicians for a variety of ailments. I believe that some thought should be given to a different role from that suggested by Dr. Goyan, namely the finding of some substitute for drug therapy.

There is little disagreement, anywhere one goes in the world, regarding the value of penicillin in certain specific infectious situations; of insulin in certain kinds of diabetes; of digitalis, in certain kinds of heart disease, etc. In other words, there is an appropriate worldwide acceptance of certain pharmacologic agents against certain specific disorders. The list if one were to develop it fully, would probably not be an overpoweringly long one. Most of the concern over drugs use has come in situations where there is no agreement regarding what drugs should be used—let alone what dose, or what response to look for. The "chemicization" of our population that is taking place both on prescription and non-prescription drugs needs an alternative.

One such alternative may be illustrated by some recent experiences. I have, in the recent past, had two patients who had come to America recently from Europe, who expressed some concern over my prescription of meprobamate for what seemed to me to be a mild tension-anxiety problem. They stated that in their country their doctor would have advised some sort of physical medicine therapy. This concept was further reinforced on a

recent trip to Russia that was undertaken to look at their health care system. Representatives of the Ministry of Health told us that we would see many things that would seem odd to us, that perhaps the most would be the widespread use of physical medicine. He then added in an aside, "We feel that this may be more appropriate than drugs, hormones, and shots." True enough in our visits to the various polyclinics and hospitals we could not but be impressed by the enormous percentage of available resources that were devoted to physical medicine. We saw individuals receiving exercise programs for hypertension, various sorts of hot baths, vapor treatments, and the like for ailments ranging from the usual musculo-skeletal disturbances to what seemed to be obvious evidences of anxiety and tension. I came away from this latter trip not sure whether physical medicine did represent an answer to this large segment of our patient population but with the feeling that others more knowledgeable about the use of such measures should look into it. It, therefore, seems to me that while there is certainly a need for an expanded role of the pharmacist as an expert in drug interactions and as a consultant to the physician in these matters there is an even more urgent need to look for alternatives to the widespread use of drugs of all sorts.

DONALD W. PETIT, M.D.
Alhambra

Report on Student Participation In Organized Medicine

*Prepared by Medical Student Representatives to the CMA
Committee on the Role of Medicine in Society*

To the Editor: Last month, for the fourth time, the California Medical Association sent medical student delegates to an American Medical Asso-

ciation Annual Convention. In light of the fact that the 1971 CMA House of Delegates voted to direct the CMA to urge other state medical societies to follow its example of having student representation on its committees and delegations, we feel it is time to review for the CMA some aspects of our past participation.

Rightly or wrongly, many students feel that they are excluded from meaningful participation in organized medicine; the automatic response is to ignore it. These attitudes tend to persist for many years, thus depriving organized medicine of a valuable source of idealistic energy. Although the AMA has seemed to hold the attitude that there is nothing wrong with this, such a schism can be to no one's advantage since basically we are both interested in the same thing—the best possible health care. The long-static structure of medical care is changing under pressure from the consumers, the people. Changes will come and, if we do not modify them constructively, do not “roll with the punch,” so to speak, they will be imposed upon us in an onerous bureaucratic structure; since we will practice under the new conditions for the rest of our lives, they are of great importance to us. At this crucial time it behooves us not to squander any of our resources.

The incorporation of students as participants both on the committees and in the delegation to the AMA of the CMA is an attempt to bridge this gap, hopefully a bellwether for future action by other state medical societies. We have ideas to contribute to the various committees of the CMA; this source is slowly being tapped to the benefit of all participants. In the course of three conventions we have progressed from being observers to working members of a regular state delegation. We have our greatest influence on current policy in the AMA by presenting our ideas to the California delegation and, if they seem to be constructive contributions, convincing it to support them before the AMA as a whole; Medical Education Community Orientation (MECO) and abortion are examples of this method of action.

If this were the sole value of our participation it might, even by itself, justify the expense of sending students to AMA conventions (an expense we try to minimize as much as possible by obtaining alternative housing with friends in the area where the convention is held). Through personal contacts between students and practicing physicians, both it is hoped become convinced that their op-

posite numbers are not the self-centered ogres it has become faddish to picture them. We are students and we are still learning, serving the beginning of our apprenticeship in organized medicine, discovering how to work within its structure and whom to work with. In the process we have developed a greater appreciation of the problems facing organized medicine. This education in the procedures and operations of the CMA and the AMA is necessary for us to be able to work effectively in those bodies as soon as possible.

One of the most critical issues facing medicine today is that of peer review and its implications (discussed in *CMA News*, Vol. 15, No. 19). Who is to judge the adequacy and necessity of medical procedures and how is he to enforce his judgment? Following inevitably upon government funds in Medicare comes the government effort to impose cost and quality controls. Blind opposition is futile in this case; too often the AMA has come across as an exclusive union concerned only with the economic and social interests of its members, thus inciting the voting public to support its elected representatives in instituting measures which are harmful to those parochial interests as well as those of health care in general. It is of prime concern that we not be subjected to a ponderous bureaucratic machine even before we begin to practice. It was encouraging that the AMA, over the last year, has seemed to become more aware of the political realities of the situation; it is only to be hoped that effective action will replace obstructionism soon enough.

In Resolution 54, which communicates to the appropriate state and federal agencies concern about the use of the pesticide Mirex, shown to be a carcinogen in mice, and urges cessation of its indiscriminate use, the AMA demonstrated its role in guarding the health of the American people. The broader ecological considerations which were hinted at in the resolution must be extended further into the areas of pollution control and population control which impinge so directly upon the health and well-being of the populace. These areas are potentially dangerous because politically sensitive, yet this should not prove a deterrent. Although there is some debate about the facts in this particular issue, there can be no doubt about the admirability of the concerns upon which the action was based. Positive action could be very valuable, showing the doctors moving when their immediate economic in-

terests are not immediately threatened. Improving the image of organized medicine, a topic much in discussion at the 1970 Annual Convention, could lead to increased leverage in helping to shape health care delivery systems, national health insurance and peer review.

We feel that the most effective way for medical students to influence AMA policies and actions and to obtain education in the machinery of organized medicine is to be a part of a regular state delegation. We would like to thank the CMA for giving us this opportunity, and we thank the AMA delegates and alternates from the many state medical associations who received us so cordially. In the future we would like to continue and expand our work, both in formulating student-initiated resolutions to be presented to future AMA conventions and in working with the CMA at those conventions. We hope that our presence has been of assistance to the California delegation.

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Magendie on Medicine

To the Editor: The clipping below is meant to ring a bell. Bell—as in Sir Charles—of course, had a dirty ring in François Magendie's ears: the two men, you will recall, fought a priority battle over the law of the nerve roots. Rooting for Ma-

*From the San Francisco EVENING BULLETIN,
September 16, 1856:*

Let me tell you, gentlemen, what I did when I was the head physician at the Hotel Dieu. Some 3,000 or 4,000 patients passed through my hands every year. I divided the patients into two classes; with one, I followed the dispensary and gave them the usual medicines without having the least idea why or wherefore;

to the other, I gave bread pills and colored water, without, of course, letting them know anything about it—and occasionally, gentlemen, I would create a third division to whom I gave nothing whatever. These last would fret a good deal, they would feel they were neglected (sick people always feel they are neglected, unless they are well drugged the fools!) and they would irritate themselves until they really got sick, but nature invariably came to the rescue, and all the persons in this third class got well. There was little mortality among those who received but bread pills and colored water, and the mortality was greatest among those who were carefully drugged according to the dispensary.

gendie, however, means to us—as it meant to some of our great-great-great grandfathers—cheers for his concept of the scientist as “rag-picker,” or collector and checker of scrappy observations. For if you are the man to present some puppies with a multiple choice of Gruyère cheese, wood, and cork, all neatly packaged (after cutting either olfactory or trigeminal nerve so as to check the respective division of labor of the two) you are also one to devise an analogous controlled experiment involving drugs and placebos offered in bread pills to patients. From the sublime of animal experimentation to the ridiculous of clinical pharmacology is, after all, only one step. And as the author of a standard “Formulary,” as well as the sentence “They are always looking for what they anticipate, never for what really is,” you were still true to yourself when you launched the movement that (via Vienna) became known as “therapeutic nihilism”—and dangerously close to Christian Science half a century later.

Magendie died in the year before the readers of the San Francisco *Evening Bulletin* became acquainted with his outrageous if pertinent views. In 1856 the crotchety pundit with a scorn for both doctors and patients was medical news of a sort. But has his message fully sunken in? After twelve decades, and much cerebrospinal fluid down through “his” foramen, we still have to admit: “Touché, Monsieur Magendie!”

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Iatrogenic Embryonic Defects— Correction of Statement Regarding Thioridazine

To the Editor: While discussing possible iatrogenic embryonic defects at the U.C. Fall Symposium on Obstetrics and Gynecology held in San Francisco (October 2 and 3, 1970), I indicated that there had been some reports of cleft palate in infants whose mothers had received thioridazine during pregnancy. This statement, however, was incorrect.

My intention was to refer to a report¹ concerning a mother who, having received phenothiazines (thioridazine and trifluoperazine) before and during pregnancy, gave birth to a child with transposition of the great vessels. A single case, of course, means little except to call for vigilance by

the clinician. Accumulating evidence, admittedly, seems generally favorable to phenothiazines and it has been stated² that there is no clinical or experimental proof that such drugs have a teratogenic effect.

Regarding cleft palate it was my intent to draw attention to a communication³ on the occurrence of this and other abnormalities in some children born of epileptic mothers who had received anticonvulsants, mostly phenobarbitone, phenytoin, primidone, or troxidone, during pregnancy. The observation is of interest but more data are required before any claim to a teratogenic effect of such drugs can be made.

I appreciate this opportunity to correct and to elaborate on my earlier statement.

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DISINFECTANTS IN COLONIC RESECTION

Is there any point in instilling antibiotics into the lumen of the nonobstructed bowel either before or after resection?

"When I resect the colon, I have the habit of using a disinfectant in the lumen of the bowel. Everybody is going to wince when I say this, but I very frequently use something like half or quarter strength Lugol's solution in the area where my clamps are or between the clamps. Antibiotics are rather feeble; they all have restricted spectra. A number of good antiseptics are available which can get rid of bacteria much better than antibiotics in topical application. I do tend to use disinfectants for this purpose. . . .

"As for preoperative preparation of the bowel, we . . . were the first or second to report an epidemic of resistant staphylococcus in the nursery which was eventually traced back to surgical patients getting neomycin bowel preps. We don't do this at all. However, I think there is a good case for preoperative bowel preparation. Your major goal should be to get rid of the stool. When you figure that each gram of stool has about 10^8 organisms and you can cut this down to maybe 10^2 or 10^3 with antibiotics, you realize that getting rid of a gram of stool is a lot better than just cutting down the bacterial content in all that's left."

—THOMAS K. HUNT, M.D., San Francisco
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The Certified Hospital Admission Program

JAMES J. SCHUBERT, M.D., JAMES BRAMHAM, M.D., FRANK SCHIRO, M.D.,
AND H. JOHN RUSH, M.D., *Sacramento*

THE MEDICAL CARE FOUNDATION of the Sacramento County Medical Society was founded and incorporated in 1958 but was not activated until 1965. The stimulus to its activation was the newly arrived presence in Sacramento of the Kaiser Health Plan. In fact when the California State Employees Association invited the Kaiser Health Plan into Sacramento as a Meyers-Geddes option for state employees, a like invitation was extended the Society to provide a Foundation plan as was available elsewhere in the state. The Society responded by activating its Foundation.

Shortly after this time there came the post-Medicare/Medicaid onslaught by segments of the public and the government directed at skyrocketing costs of health care and the so-called "non-system" of health delivery. In this atmosphere of concern, the Sacramento County Medical Society sponsored for its elective and appointive officers a day-long retreat to study the pressing problems of medicine in general, but in particular the problems of medicine as related to our community. One of the many by-products of this retreat was the Foundation Coordinated Health Plan and with it the Certified Hospital Admission Program (CHAP). The Society Board of Directors asked the Medical Care Foundation to develop a comprehensive private health insurance plan that could be presented at a reasonable competitive premium, that would allow for free choice of physician and hospital, that would be adaptable

to various consumer groups, and that could be supported by the medical profession and the insurance industry while maintaining the principle of fee-for-service.

It was felt necessary to find some mechanism whereby significant savings could be made which would pay for the additional benefit structure. Almost simultaneously, Mr. Leon Hyman, a vice president of California-Western States Life Insurance Company of Sacramento, approached the Medical Care Foundation with his concept of pre-admission review and length of stay monitoring. At first we felt that this concept would be unacceptable to both the physician and the patient; however, studies have shown a significant variance in the hospital days used per year under various insurance carriers. For example, Cal-West reported a high of 1000 days per 1000 insured per year, the Blues about 875:1000 and Kaiser approximately 515:1000. Among the factors affecting the length of stay and incidence of hospitalization is the severe limitation some insurance plans place on outpatient benefits. Hence diagnostic admissions often occur in order to obtain coverage for services which otherwise could have been obtained in the office or outpatient laboratory. It was the aim of the comprehensive Foundation Coordinated Health Plan to insist on total outpatient benefits, including outpatient medical and surgical benefits, diagnostic laboratory and x-ray, annual examination, immunization, newborn care, and the like, and thus eliminate the need for diagnostic admissions. In closed panel plans, because of capitation factors, length of stays are closely controlled.

Over a period of time our joint task force de-

President, Medical Care Foundation of Sacramento (Schubert); Past President, Medical Care Foundation of Sacramento, and President-elect, Sacramento County Medical Society (Bramham); Chairman, Committee on Research and Development of the Medical Care Foundation of Sacramento (Schiro); Chairman, CHAP Committee, Sacramento County Medical Society (Rush).

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veloped our Foundation Coordinated Health Plan and the Certified Hospital Admission Program, which we call CHAP. Local area hospital administrators helped develop the methods and procedures which are part of CHAP. Without their cooperation and support this program would never have developed, let alone succeed.

CHAP is defined as a prospective hospital utilization program combining pre-admission and concurrent peer review to determine medical necessity for hospital admission and length of stay.

The basic mechanisms of this program include:

- (1) Pre-admission notification of the Foundation by the attending physician, when elective procedure and elective admission will occur.
- (2) The diagnosis and/or planned surgical procedure is matched against community length of stay norms developed by the Foundation over a period of years.
- (3) The physician and hospital are notified that a predetermined hospital length of stay for that diagnosis will be certified for payment without further retrospective audit.
- (4) The patient's physical condition is monitored by a Foundation Nurse Coordinator *during hospitalization*.
- (5) Should the patient's physical condition change, the length of stay certification period will be adjusted to satisfy the needs of the patient and the attending physician.
- (6) Emergency admissions do not require pre-admission notification, but the Nurse Coordinator employed by the Foundation monitors the patient's condition after the admission has occurred. Medical advisors in each practice field appointed by the Foundation are used as consultants to screen hospital admissions where there is some question as to the medical need for hospital services, and to certify extensions of length of stay beyond the norms which we have previously discussed.

The essence of this program is that a Foundation physician may certify the medical necessity for his own hospital admission by notifying the Foundation in advance and putting his admission through a pre-admission screening procedure. The patient's physical condition is monitored while in the hospital, and the hospital is then guaranteed payment for this admission. In April, 1970, when the State Medi-Cal program was placed on prior authorization by the Department of Health Care Services, the Sacramento area was thus designated a demonstration area for the CHAP program for Medi-Cal beneficiaries. Some 80,000 Medi-Cal beneficiaries in the Sacramento area

are currently monitored through the CHAP Medical Project. All admissions of Medi-Cal beneficiaries to hospitals in the Sacramento area must be certified by the Foundation in order for the hospital to receive payment through the fiscal intermediary, Blue Cross. At the time of discharge, a certified form is attached to the hospital bill, which is forwarded to the fiscal intermediary for payment. (If the bill is received without a CHAP certificate, the hospital bill is denied.) There are no further audits, retrospective denials and long periods of review. The determination of medical necessity has been completed as far as the hospital is concerned through the CHAP certification procedure.

This program, as mentioned above, was first used in a private health insurance plan which was underwritten by California-Western States Life Insurance Company for a local printers' union. Some 2000 lives were enrolled in this plan and it operated for about six months before this program was extended to the Medi-Cal beneficiaries. In the printers' union we found a significant reduction in the number of hospital days used per 1000, which resulted in a decrease of 18 percent in hospital expenditures. The effect of the CHAP program on Medi-Cal admissions is currently being studied by the California Health Data Corporation and by the Medical Care Foundation. It is planned that the results of this program will be published in the near future.

One might quote from a statement made by George Meany, president of the A.F.L.-C.I.O., in testimony before the United States Senate Labor and Public Welfare Committee on proposed national health insurance legislation. Mr. Meany said: "American industry is accustomed to rational management, efficient administration, careful cost control, and high productivity. But the medical industry has not the most rudimentary idea of how to achieve these things. It is time that modern American medicine find 20th century methods for delivering health care."

We believe that the Certified Hospital Admission Program is one step in the progressive development of a medical management system for and by private medicine. The Sacramento Medical Care Foundation feels that it is only through experimental programs such as CHAP, and numerous other innovative programs involving peer review at the local level, that private medicine as we know it will survive in the health world of the future.

The Practice of Medicine in the Bush Country of Ghana

The next time nothing seems to happen when you order STAT ARTERIAL gases or cardiac enzymes, you might like to imagine how things would be if you were practicing in the bush country of West Africa.

Recently I have had a chance to consider the "hardships" of practice in California, as the result of a letter from Ghana. My correspondent was Marlene Long, M.D., a graduate of Howard University College of Medicine. After medical school, Dr. Long interned in San Francisco and then took additional training at Queen of Angels Hospital in Los Angeles. Part of her report from Africa is given below.

B. HUGH BUFF, M.D.
San Diego

. . . Greetings from the "bush" of northern Ghana—namely, Nandom, a little town (more accurately, a group of village compounds) in the northwest corner of Ghana near the border of Upper Volta along the Black Volta River. I have been out here over two and a half years, serving as a medical missionary. What is it like? Unless you've done tropical medicine, you may have no idea. I must say there's nothing like it, and I love it immensely.

This mission was established about 1929 by the White Fathers, mostly Canadians at that time, in a pagan environment among the Dagarre tribe. Today, the Dagarre are still not advanced technologically, but are mostly Christian and making rapid strides socially. As Ghana is very poor—though with great potential—and still rife

with tribalism (as is most of Africa), this section in the North gets little attention from the central government 500 miles away in Accra in the South, on the beautiful Gulf of Guinea. So most of the people (except for a *very* small half-educated minority) live in what we Americans would call primitive conditions—i.e., mud huts, no sanitary facilities, water from a muddy, contaminated stream or pond. The people wear little or no clothes; agriculture consists of work with a short-handle bent hoe and at the mercy of the elements. Under such conditions, you can imagine the problems one has to face to get over the simplest aspects of personal and communal hygiene, let alone preventive medicine! Curative medicine our patients understand, as they come with a pain and go away better (*usually, if they come in time*).

One comes out to "give," and one does; but what one receives from these poor of God is beyond price. There is spiritual richness in the midst of their material poverty. An old man standing before you, wearing only a loincloth and with a hoe over his left shoulder, commands a certain respect. He has the pride of a president, and perhaps more personal dignity before God and man. This is hard to explain, but important. We Americans are so efficient and busy and professional; we too often forget that patients are more than anatomy, physiology, and lab results. They are human—real people, "made in the image and likeness of God." These people have a way of being that reminds the doctor one must treat the whole man, not just symptoms. If you don't consider the "whole man"—his place in his compound, his relations, his culture and beliefs—you'll miss the boat, and sometimes the di-

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agnosis with it! The Dagarre are not fast or efficient, but this doesn't mean that they're dull-witted. They think long but deep, and act (maybe a bit slowly) if they consider it necessary.

I work with five White Sisters—two Canadian, one American, one English, and one Scottish—in a 40-bed Health Centre, with 11 maternity beds. “Officially,” it doesn't have hospital status, but we don't care. We've 60,000 people to serve, from about five different tribes; they have nothing else—so we do our best to run it as a hospital. There are about 40-45 employees, including laborers, launderers, tailors, stock boys, and clerks. There is only one African RN; two of the Sisters are RN-Midwives—the others are just trained midwives. (I don't do any deliveries out here unless by forceps or C-section.) We have five African QRN's—these are halfway between our LVN's and RN's. Some of them can be pretty good, *practically* speaking, but they've only had about a Junior High level of education—if that much. The only science and “advanced math” they get is in their nursing training.

We've seven Ward Assistants—less trained than our orderlies; then there are two Dressers—an occupation I think unique to underdeveloped countries. They are trained in simple first-aid (more or less) and to treat some disorders—fever and diarrhea and headache (the last most likely due to malaria, and the diarrhea to amebae). The Dressers can identify a worm passed per rectum (the patient will bring it in and show it to you) and prescribe the appropriate treatment. These Dressers are usually posted to Dressing Stations in villages where there's no hospital or Health Centre. As we're short-staffed, we employ them to serve various functions. One I've trained as a lab technician, from real scratch (about a 6th-8th grade education, and no science at all). We've a boy who dispenses the medicines—grade-school education, but has learned a lot by doing.

We treat mostly malaria—all times of the year, more in the rainy season; various dysenteries, usually due to amebae and flagellates; and a host of intestinal and bladder parasites—hookworms, roundworms, tapeworms. (A couple of days ago, a woman came to us for treatment. She brought with her a large Excedrin® bottle, which contained the tapeworm she'd passed the night before. The worm was about six feet long, intact!)

—And pinworms, threadworms, flukes, ad infinitum.

There's anemia—mostly due to malnutrition, or just plain starvation. We see the same skinny pot-bellied children that you saw in news pictures from Biafra. It's not a “Biafran disease.” People, especially children, are starving everywhere. It's our biggest medical-social-economic problem. True, I prescribe tons of vitamins and iron, but it's frustrating, because I realize that the crux of the problem lies in the lack of proper diet and hygiene.

There's a great need for health education. It is hard to break custom. Until they're two years old and walking about, children pull on their mothers' wrinkled breasts. Many of the children don't survive, just for that reason. The breast milk of their anemic, undernourished mothers doesn't supply the needs of growing children from six months to two years old. But the village women (even some nurses) can't seem to realize this. On the other hand, if a mother doesn't put the breast in her child's mouth when he's crying, what can she give him? Nothing! At certain times of the year—around the end of the dry season (March-May)—there's just no food to eat. You may talk all you want to about “balanced diets”—fresh vegetables, meat, eggs, etc. They'll only look at you, because all they have is a bit of maize porridge—*maybe*. They make that go as far as possible by having the adults eat every other day or so and giving the children a few mouthfuls each day—either in the a.m. or in the evening, not at both times. It is something to ponder when we sit down to a nice chop or steak, vegetables, all the rest.

The solution to this “medical” problem is basically agricultural. They just don't grow enough food. So one must be not only a clinician but teacher and dietician, and know a bit about how the native farms, and be able to offer a little discreet humble advice on the side—e.g., having an “off-season” garden to grow a few “greens” for some minerals in the diet, etc.

We see onchocerciasis—from a parasite that invades the lymphatics and the eyes (causing blindness). It also gives rise to firm subcutaneous nodules which patients often want removed—not for cosmetic reasons, but because they believe the nodules cause various maladies (headaches,

joint pains, etc.). I trained my "surgical assistants" from scratch while removing these nodules. We have another worm, filaria, which blocks the lymphatics and causes the classical elephantiasis. We don't see much of that out here these days, as many natives have been receiving treatment over the past 30-40 years.

The Africans also suffer from colds, earaches, tonsillitis (rare among children here), pneumonia, measles (*deadly* among children ages six months to three years), croup, adenitis of all types. Infections are common, because of the living conditions and lowered resistance. Very common is the tropical ulcer or open sore on the lower legs, ankles, and feet that just "never heals." Then there is tropical pyomyositis or "muscle abscess"; it's just that—an abscess in thigh, calf, shoulder muscle, etc. The patient suffers intensely, and may become quite septic or

even die. I've seen two young men die from this, and three others come close to death. It's something to stick a blade in a thigh and get out enough pus to fill at least a couple of large kidney basins. Various dermatitides abound. I can't begin to name them. Also osteomyelitis, carbuncles, furuncles, cellulitis.

Surgery is mostly hernia repair—usually in males of course, but I've done quite a few female inguinal and femoral herniae. Then hydroceles—containing perhaps a liter of fluid; C-sections; removal of subcutaneous nodules, lipomas, and scalp wens. On the orthopedic side, there are trauma cases (e.g., fractures, amputations). My nurses suture the minor lacerations. Well, enough for now. . . .

MARLENE E. LONG, M.D.
(Written while stationed at
Nandom Hospital, Nandom,
Ghana, West Africa)

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PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H., Director, State Department of Public Health

Air Pollution, Health Effects and Urban Growth

AIR POLLUTION REPRESENTS a serious public health problem in California, and the state has taken a paramount role in studying it. Since 1954 the State Department of Public Health has conducted research on the effects of air pollution on health, and the application of such research to determine what upper limits need to be imposed on pollutants to protect the public health. The first scientifically supported air quality standards in the nation were developed by the department in 1959; and the first air quality standards of the nation, recently announced by the National Environmental Protection Agency, are similar to California's new standards, which themselves are based on the department's recommendations.

Air quality standards are of two types, one based on health preservation and the other on esthetic values and the protection of property. Most of the state and federal standards are based on health considerations. The staff of the State Department of Public Health has investigated, among other health reactions, the effects of oxidants on asthma¹ and lung function² and has carried out research on the body burdens of lead³ and carbon monoxide⁴ and their implications for health. In recent years, 1969 and 1970, the department has undertaken a major review of research in setting standards in conjunction with

the California Air Resources Board. In this work the department has used the advice and support of many experts in this field.

At the start of the efforts toward air pollution control, we did not know how much reduction in per capita pollution was possible or likely. Recently, however, the Technical Advisory Committee to the Air Resources Board made a detailed investigation as to the likelihood of achieving established air quality standards.

The committee reports that in some parts of the state air pollution standards cannot be achieved by applying technical methods available now or in the foreseeable future *if present growth trends continue*. We do not know how to control pollutant emissions enough to reach these standards. Therefore, if reduction in pollutants acceptable from the health viewpoint are to be reached or maintained, major changes in air pollution control plans must be made. This is true in some of the state air basins because of the size and growth rate of the population and the number of emission sources.

For example, the Technical Advisory Committee states that although the recommended hourly average oxidant standard for Los Angeles is 0.1 parts per million (ppm), and the federal law requires that federal air quality standards, 0.08 ppm, be met by May 1975 throughout the nation, the values will probably not, with present and planned controls, be below 0.25 to 0.35 ppm by 1980. Even by 1985 the oxidant level in Los Angeles will probably remain as high as 0.20 to 0.25.

The committee further suggests that it will not be possible to reach the oxidant standard of 0.1 ppm in Los Angeles by programs designed only to limit emissions from sources now anticipated on the basis of existing growth patterns. More drastic measures are needed, involving limiting the number and use of automobiles, trucks and

aircraft in the air basin and reducing emissions from these sources to levels below those now proposed. It would also be necessary to establish emission-free industries and fossil-fuel power plants, to develop a non-polluting urban transport system, and to limit population growth by restricting subdivision and residential expansion in the basin. Otherwise, people will continue to be exposed to oxidant levels which will have deleterious effects on their health. Some are even more concerned with the present health effects of carbon monoxide. For example, a State Health Department study based on daily mortality figures for Los Angeles for a four-year period from January 1 1962 through December 31 1965⁵ showed that carbon monoxide in concentrations encountered in Los Angeles, was associated with a small but significant contribution to daily death rates.

What, then, can be done to reduce health hazards from air pollution?

Any such efforts include three components. One is the short-range, immediate "air pollution health warning system," which warns the population, especially persons susceptible to respiratory disease, of hazards during a severe pollution episode. This program is carried out with the cooperation of local physicians and health officers in conjunction with the appropriate committees of the California Medical Association.

The second is a continuing effort to apply forcefully and diligently available technologic knowl-

edge to reduce emissions from all sources of air pollution to the maximum feasible extent.

As the Air Resources Board Technical Advisory Committee has made clear, however, technology alone without significant changes in our mode of life will not provide air of sufficient purity to avoid deleterious effects on health. Accordingly, a third component must be long-range community planning which considers the number and sources of pollutant emissions and, by inference, the population of an air basin, along with the amount of pollution from each source. Communities should develop long-range policies for land use, power generation, transportation, and limitations on population density which would prevent pollution and which would result in other desirable health effects as well. The State Department of Public Health will encourage and support such efforts, and hereby goes on record as being opposed to developments that would increase air pollution loadings in our critical air basins.

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EYEBROW PULLING IN CHILDREN

How do you manage an otherwise normal ten-year-old boy who picks out his eyebrows and lashes?

"This is a habit, and there are lots of habits that we get very concerned about. We used to get very concerned about thumbsucking; and we used to get concerned about nail biting . . . until somebody did a survey and found that 80 percent of all children go through a period of nail biting during their growing up. Ten years old is also the age when you will see ties in children. Most of these habits are self-limited. The important part is the family's response. The more upset the family gets about this the more likely there is to be a long-range problem. It becomes a vicious circle. The suggestion to the child that he do it only in his own room and not in public might be one way to minimize the family's reaction. I think that in 99 out of 100 cases this habit will come to an end all by itself."

—HANS R. HUESSEY, M.D., Burlington
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Information

Congenital Heart Disease In the First Year of Life

SIDNEY BLUMENTHAL, M.D., AND
MARY JANE JESSE, M.D.

*Material Supplied by the American
Heart Association*

SURGICAL ADVANCES in the past two decades in the management of patients with congenital heart defects have been truly spectacular. These results have been achieved for the most part in older children and adults. It is somewhat sobering to note, however, that 95 percent of deaths due to these defects occur in the first year of life, most in the first six months. Twenty percent of patients with congenital cardiac defects develop congestive heart failure; 90 percent of these patients are less than one year of age. The present thrust must be directed toward the treatment of the young infant. To ensure success, an aggressive approach is necessary in which the physician supplying "first-line" care (generalist or pediatrician) becomes a participant in the team which includes the pediatric cardiologist and cardiovascular surgeon. Pediatric cardiologists and cardiovascular surgeons are, for the most part, aware of their role. The "first-line" physician needs to recognize his role as an active participant so that infants in jeopardy will be recognized and treated early or the total endeavor is doomed to failure.

A small number of anomalies are responsible for congestive heart failure or death in most infants. Palliative or corrective surgery in infancy is available for infants with anomalies listed in

Table 1, while there is no surgical relief for those with anomalies listed in Table 2, as well as in some of the more complicated lesions seen less frequently.

It is not essential for the generalist to make an exact anatomical diagnosis; this is required of the pediatric cardiologist. Identification of the infant in early heart failure and those with a predisposition to hypoxic "spells" or sudden death is the generalist's chief role. This will enable him to identify the infant requiring emergency or early referral to a center equipped and staffed to perform the necessary diagnostic studies with a minimum of risk to the infant.

All infants known to have a congenital cardiac anomaly should be followed closely during the first six months, their period of greatest risk. Most do not require referral to a large center. The thriving asymptomatic infant should have an electrocardiogram and x-ray of the chest performed at about one month of age. If these are normal, subsequent referral may be indicated on an elective basis.

Emergency referral to a center is indicated for infants who show signs of congestive heart failure or in whom the electrocardiogram reveals a "strain" pattern of either left or right ventricle. In the cyanotic infant, emergency referral is indicated in those with a history of hypoxic "spells," respiratory distress, evidence of pulmonary plethora in the chest film or right ventricular "strain" in the electrocardiogram. Procrastination results in decreasing myocardial function resulting from hypoxia and acidemia.

Congestive heart failure in the infant is usually insidious in onset. Decreased cardiac output results in fatigue usually manifested by feeding difficulty. The infant sucks eagerly, but fatigues after

**TABLE 1.—Anomalies Amenable to
Surgical Correction**

<i>Acyanotic</i>	<i>Cyanotic</i>
Vent. Septal Defect	Tetralogy Fallot
Atr. Septal Defect	Transposition Complex
Patent Duct. Art.	Tricuspid Atresia
Coarctation Aorta	Pulmonary Atresia
Pulmonic Stenosis	Total Anom. Pulm. Veins
Aortic Stenosis	

TABLE 2.—No Available Surgical Relief

Hypoplastic left heart syndrome
Endocardial fibroelastosis

The authors are from the Department of Pediatrics, College of Physicians and Surgeons, Columbia University, New York City.

taking a few ounces of formula. He soon becomes hungry, takes a few more ounces and falls off to sleep. A vicious cycle develops, easily confused with intolerance to formula, "colic" and "failure to thrive." Grey, mottled cold extremities indicative of vasoconstriction are a homeostatis response to an inadequate cardiac output.

Tachypnea is usually the earliest manifestation of heart failure in the infant. Pulmonary venous congestion secondary to left heart failure is manifested by tachypnea. Respiratory rates over 50 a minute are abnormal in the quietly resting infant. Those in failure commonly exhibit respiratory rates of 60-100 a minute, and at times, 120-150 a minute. In addition to tachypnea, one may note intercostal and sternal retraction and eventually bronchial congestion with cough and bronchospasm. Rales, in the absence of infection, are only seen in late stages of heart failure. Tachypnea is accompanied by tachycardia and often a gallop rhythm heard best about 0.10 seconds after the second sound, often resembling a third heart sound. Pulmonary venous congestion may be identified on the x-ray film by hilar shadows, at times extending to the periphery of the lung.

Systemic venous congestion secondary to right heart failure is manifested by hepatomegaly, the liver edge extending more than 4 cm below the costal margin. Tenderness is uncommon. Pitting edema and neck vein distention are not usually apparent.

Heart failure of sudden onset is uncommon in infants. It may result from an acute myocarditis, dysrhythmias or myocardial infarction.

"Spells" are seen most often in infants with tetralogy of Fallot. About 10 percent end in fatalities and an equal number are complicated by cerebrovascular accidents. "Spells" are characterized by sudden onset of dyspnea, irritability and a marked increase in degree of cyanosis. The

infant becomes limp, may convulse and/or lose consciousness. Spells are associated with temporary disappearance of a pre-existing murmur, decreased arterial oxygen saturation and ST depression with increased p wave voltage in the electrocardiogram. Spells may be seen in very early infancy, becoming most common around nine months of age and decreasing in frequency after eighteen months. They often occur without warning but may be precipitated by crying, fever or hot weather. "Spells" should be treated by placing the infant in the knee-chest position, administering oxygen and morphine (0.2mg/Kg). Urgent referral for diagnosis and surgical relief is indicated.

The possibility of sudden death due to critical aortic or pulmonic stenosis should be considered in any infant with electrocardiographic evidence of left or right heart "strain" patterns. It behooves the generalist to recognize these patterns as his minimum requirement in pediatric electrocardiography.

Several types of cyanosis may be seen in infants. Peripheral cyanosis due to vasoconstriction is associated with cold, mottled extremities. Harlequin cyanosis has no clinical significance, being common in normal infants during the first week of life, and may be seen as late as 28 days. It is confined to one half of the body with strict midline demarcation. More commonly, it is manifested by pallor or redness but semicyanosis may be the presenting feature. Cyanosis due to pulmonary disturbances or right to left intracardiac shunting may be difficult to differentiate on clinical grounds if accompanied by respiratory distress. In the absence of respiratory distress the cause is most apt to be a right to left shunt. We believe that an anatomical diagnosis should be made in all cyanotic infants, but not necessarily on an emergency basis.

In Memoriam

ABBETT, ARTHUR LOUIS, Del Mar. Died April 4, 1971 in San Diego of myocardial infarction, aged 64. Graduate of University of Minnesota Medical School, Minneapolis, 1935. Licensed in California in 1935. Doctor Abbett was a member of the Alameda-Contra Costa Medical Association.

**

EMERY, CLAUDE E., San Francisco. Died May 25, 1971 in San Francisco, aged 76. Graduate of the University of California Medical School, Berkeley-San Francisco, 1924. Licensed in California in 1924. Doctor Emery was a member of the San Francisco Medical Society.

**

GRAY, PERCIVAL A., JR., Santa Barbara. Died May 16, 1971 in Santa Barbara, aged 71. Graduate of Rush Medical College, Chicago, 1927. Licensed in California in 1928. Doctor Gray was a retired member of the Santa Barbara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

**

LUDWIG, CHARLES H., Fresno. Died April 30, 1971 in Yosemite National Park, aged 50. Graduate of University of California Medical School, Berkeley-San Francisco, 1946. Licensed in California in 1946. Doctor Ludwig was a member of the Fresno County Medical Society.

**

MARTIN, JERRY GENE, Rodeo. Died May 8, 1971 in Rodeo, aged 31. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1964. Licensed in California in 1967. Doctor Martin was a member of the Alameda-Contra Costa Medical Association.

**

MCGOVERN, BERNARD E., Los Angeles. Died April 30, 1971 in Santa Monica of coronary artery disease, aged 77. Graduate of University of Nebraska College of Medicine, Omaha, 1920. Licensed in California in 1935. Doctor McGovern was a member of the Los Angeles County Medical Association.

**

MILHOLLAND, WILLIAM GEORGE, Pebble Beach. Died May 8, 1971, aged 77. Graduate of Tulane University School of Medicine, New Orleans, 1921. Licensed in California in 1921. Doctor Milholland was a retired member of the Fresno County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

**

MILLS, STEPHEN ROY, San Diego. Died May 6, 1971 in San Diego of heart disease, aged 49. Graduate of George Washington University School of Medicine, Washington, D.C., 1947. Licensed in California in 1959. Doctor Mills was a member of the San Diego County Medical Society.

**

NICOLA, TESLA CASE, Alhambra. Died March 15, 1971 in Loma Linda of brain tumor, aged 74. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1924. Licensed in California in 1924. Doctor Nicola was a member of the Los Angeles County Medical Association.

**

NOLAN, FRANK GREGORY, Los Angeles. Died May 22, 1971 in Glendale of bronchogenic carcinoma, aged 66.

Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1933. Licensed in California in 1934. M.D. degree from California College of Medicine, 1962. Doctor Nolan was a member of the Los Angeles County Medical Association.

**

OLSEN, SIDNEY, San Francisco. Died April 21, 1971, aged 80. Graduate of University of California Medical School, Berkeley-San Francisco, 1918. Licensed in California in 1918. Doctor Olsen was a member of the San Francisco Medical Society.

**

PARHAM, BEVERLY BLUNT, Santa Monica. Died February 13, 1971 in Santa Monica of heart disease, aged 47. Graduate of the University of the Philippines College of Medicine, Manila, 1951. Licensed in California in 1953. Doctor Parham was a member of the Los Angeles County Medical Association.

**

PIMENTEL, GEORGE BRAZIL, Los Banos. Died April 16, 1971 in Los Banos, aged 67. Graduate of Loyola University School of Medicine, Chicago, 1931. Licensed in California in 1931. Doctor Pimentel was a member of the Merced-Mariposa Medical Society.

**

PINESS, GEORGE, Beverly Hills. Died December 26, 1970 of myocardial infarction, aged 79. Graduate of Baltimore Medical College, 1913. Licensed in California in 1915. Doctor Piness was a member of the Los Angeles County Medical Association.

**

ROE, HAROLD EWART, Pomona. Died April 23, 1971 in Pomona of a cerebral vascular accident, aged 71. Graduate of the University of Minnesota Medical School, Minneapolis, 1930. Licensed in California in 1933. Doctor Roe was a member of the Los Angeles County Medical Association.

**

SHROPSHIRE, LEE, Claremont. Died December 17, 1970 in Pomona of pulmonary embolus, pulmonary emphysema, and asthmatic bronchitis, aged 58. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1945. Licensed in California in 1945. M.D. degree from California College of Medicine, 1962. Doctor Shropshire was an associate member of the Los Angeles County Medical Association.

**

SINGMAN, DAVID, Berkeley. Died May 5, 1971 in Berkeley of heart disease, aged 58. Graduate of University of California Medical School, Berkeley-San Francisco, 1938. Licensed in California in 1938. Doctor Singman was a member of the Alameda-Contra Costa Medical Association.

**

SIPPLE, LEDLEY M., Los Angeles. Died January 3, 1971 in Los Angeles of cerebrovascular accident, aged 59. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1934. Licensed in California in 1934. M.D. degree from California College of Medicine, 1962. Doctor Sipple was a member of the Los Angeles County Medical Association.

**



Oral Therapy of Diabetes Insipidus With Chlorpropamide

WILLIAM G. CUSHARD, JR., CAPT, USAF, MC, CHARLES J. BEAUCHAMP, LT COL, USAF, MC,
AND NEIL D. MARTIN, LT COL, USAF, MC, *Travis Air Force Base*

■ *Chlorpropamide was found to be an effective antidiuretic agent in vasopressin-sensitive diabetes insipidus. Full clinical use of this action is limited by the frequent occurrence of hypoglycemia on higher doses. This complication can be avoided, however, by restricting the dose and by employing combination therapy with hydrochlorothiazide.*

THE ANTIDIURETIC EFFECT of chlorpropamide was discovered, by serendipity, in Brazil when a patient with diabetes insipidus wrongly treated himself for diabetes mellitus with this drug.¹ The striking results were subsequently reproduced in other patients with true diabetes insipidus by investigators in several countries.^{2,3,4} Detailed studies in some fifty patients have now been reported with overwhelmingly favorable conclusions.⁵ It seems that most patients with diabetes insipidus can now be treated orally;⁶ in only the most severe cases is injectable vasopressin required.

The purpose of this report is to call attention to these recent developments, to describe our own experience, and to point out the side effects which may occur.

Materials and Methods

Eight patients, including three children, with diabetes insipidus of various causes were studied

Endocrinology Service (Cushard); Chairman, Department of Pediatrics (Beauchamp); Chief, Internal Medicine Service (Martin), David Grant USAF Medical Center, Travis Air Force Base.

The views expressed herein are those of the authors and do not necessarily reflect the views of the U.S. Air Force or the Department of Defense.

Submitted, revised, October 26, 1970.

Reprint requests to: 525 Hawthorne Place, Chicago, Ill. 60657 (Dr. W. G. Cushard, Jr.).

(Table 1). Diagnosis was established by standard water deprivation tests^{7,8} or the Hickey-Hare maneuver,⁹ or both. Complete endocrine evaluation, including assessment of gonadal, thyroid and adrenocortical function, had previously been accomplished. Skull x-ray studies, carotid arteriograms and pneumoencephalograms were done in most cases, as indicated. All patients responded normally to parenteral vasopressin. This medication was then discontinued and 24-hour urine volumes were measured while the subjects were taking water, salt and food ad libitum. Essential hormone replacement therapy with thyroxine and hydrocortisone was continued throughout this investigation. After baseline urine volumes, urine and serum osmolality, serum electrolytes and creatinine clearances were obtained, treatment with oral chlorpropamide was begun. Doses between 125 and 1,000 mg were employed, using a once a day dosage schedule, and allowing at least three days at each dose level. Twenty-four hour urine volumes, urine and serum osmolality, electrolytes, creatinine clearance and fasting blood glucose levels were repeatedly determined during treatment. In most cases, water deprivation tests were performed during treatment to demonstrate maximal urine concentrating ability.

TABLE 1.—Data on Eight Patients Treated with Chlorpropamide by Mouth for Diabetes Insipidus

Sex	Age	Height (Inches)	Weight (Pounds)	Illness Duration	Mean Daily Urine Volume (Liters/24 hr.)	Creatinine Clearance (ml/min.)	Etiology	Associated Endocrine Deficiency
M	40	72	225	2 Years	10.7	79	Suspected pinealoma	Hypogonadotropic hypogonadism
M	10	47	55	4 Years	5.4	110	Craniopharyngioma	Panhypopituitarism
M	18	67	164	5 Years	5.5	92	Craniopharyngioma	Panhypopituitarism
F	12	63	117	9 Years	5.8	125	Idiopathic	No other defects
M	13	62	117	5 Years	7.1	130	Histiocytosis X	No other defects
F	45	63	134	17 Years	10.0	69	Idiopathic	No other defects
M	20	72	172	6 Months	10.5	103	Idiopathic	No other defects
F	31	66	140	8 Months	8.6	144	Idiopathic	No other defects

Results

Untreated 24-hour urine volumes ranged from 5.4 to 10.7 liters. In five of six patients treated with chlorpropamide alone, daily urine volumes were reduced to less than 2 liters (Chart 1). In the sixth, urine excretion was reduced from an untreated volume above 10 liters, to less than 3 liters. In the seventh, treatment with chlorpropamide combined with hydrochlorothiazide decreased her daily urine volume from 10 to less than 2 liters (Chart 2). Although thiazide therapy produced remarkable antidiuresis, the addition of chlorpropamide to her regimen resulted in further reduction of her urine output to a completely satisfactory level. Only patient

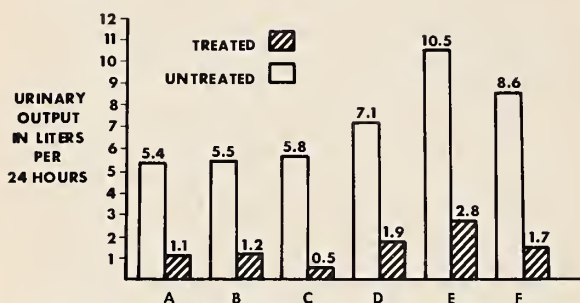


Chart 1.—Antidiuretic effect of chlorpropamide. These patients were treated with chlorpropamide, 500 mg daily. The resulting antidiuresis is shown by the shaded bars.

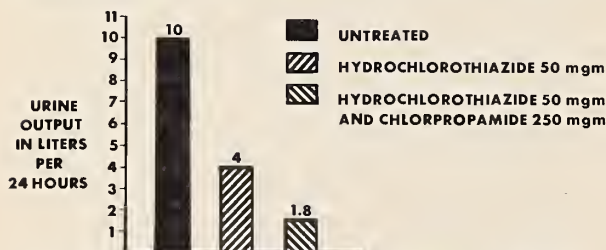


Chart 2.—Results of combined oral therapy with chlorpropamide and hydrochlorothiazide (Patient G).

H, with an average daily urine volume of nearly 11 liters, was refractory to chlorpropamide therapy. His treated urine volume remained two-thirds of his untreated volume, in spite of hypoglycemic doses of chlorpropamide (Chart 3). Fortunately, hydrochlorothiazide was of considerable benefit in this case.

In most cases, there was a three to four day lag before maximal antidiuresis was achieved. Also, the antidiuretic effect seemed to be dose-related, as indicated in Chart 4.

During treatment with various doses of chlorpropamide, serum osmolality was maintained within the normal range. Urine osmolality was consistently hypertonic with respect to serum whenever a satisfactory degree of antidiuresis was achieved. A decided increase in urine osmolality was demonstrated by water deprivation tests during therapy. More importantly, these treated patients were able to undergo 12-hour and 18-hour water deprivation tests without development of symptomatic dehydration. Excellent water conservation was demonstrated by the lack of significant weight loss and by the preservation of normal serum osmolality during water deprivation.

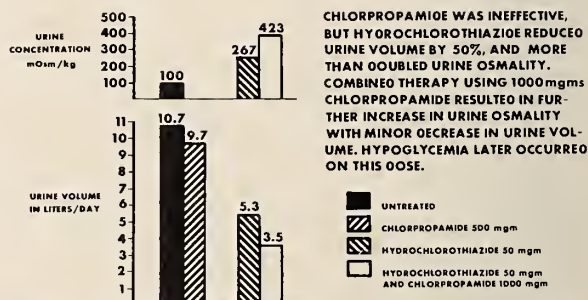


Chart 3.—Results of treatment with both chlorpropamide and hydrochlorothiazide (Patient H).

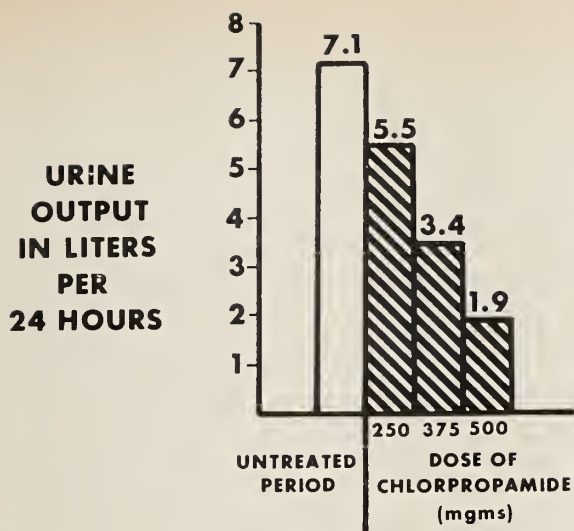


Chart 4.—Patient J was treated for three days at each of three dosage levels. Increasing antidiuresis resulted appeared to be dose-related.

Side Effects

Hypoglycemia of varying degrees was observed in almost all cases at some time during investigation of the drug, and it was used as the end point to judge dose-effect relationships. This was generally the limiting factor, as further antidiuresis could usually be achieved at the expense of hypoglycemia. For example, patient C felt well on 250 mg with a 1.6 liter average urine output. On 500 mg her urine volume further decreased to 0.5 liter but intolerable hypoglycemia soon developed. Patient G was symptomatically hypoglycemic on 500 mg of chlorpropamide, but felt well on 250 mg plus 50 mg of hydrochlorothiazide daily. The latter drug not only reduced her urine volume, but was thought to be beneficial in protecting her from chlorpropamide-induced hypoglycemia.

In most cases, however, the antidiuretic dose was substantially less than the hypoglycemic dose, thus allowing general acceptance of the drug as an antidiuretic agent. The doses used to achieve maximal antidiuresis (Chart 1) tended to cause hypoglycemia after the patient had been discharged from the hospital, and for that reason were subsequently reduced with slight sacrifice in water conservation. However, the values given do serve to demonstrate the profound antidiuretic action of this drug.

Hyponatremia with symptoms of water intoxication (inappropriate antidiuretic hormone [ADH] effect) was not observed during this study and is

mentioned only because it has recently been reported as a complication of chlorpropamide therapy.¹⁰

Discussion

Treatment of diabetes insipidus with vasopressin in various forms (parenteral, snuff, nasal spray) is not infrequently attended by unpleasant allergic or idiosyncratic local reactions. Although true refractoriness to vasopressin is uncommon, it was encountered in the present series with use of both vasopressin tannate injection and lysine-8-vasopressin nasal spray and served as motivation to attempt other forms of therapy. Despite its effectiveness in most cases, vasopressin is generally a nuisance, at best. However, patients with severe deficiency of vasopressin, as manifest by high grades of polyuria and polydipsia, are obligated to accept this nuisance if they are to live normally.

The first* oral form of treatment was reported in 1959 by Crawford and Kennedy who used chlorothiazide¹¹ and hydrochlorothiazide.¹² These drugs increased the osmolality of urine and reduced the daily excreted volume by about 50 percent. Since that time, thiazides have become a widely used adjunct in the management of diabetes insipidus and the mainstay of treatment of nephrogenic diabetes insipidus.¹³ The mechanism of action has been disputed.¹⁴ It is unlikely that significantly increased permeability to water of the distal nephron results (ADH-like effect) since the resulting urine never becomes hypertonic.

In contrast, consistently hypertonic urine is achieved during treatment with chlorpropamide. This finding is consistent with reduction of free water clearance as demonstrated by Hocken and Longson¹⁵ in their patient on treatment with chlorpropamide. The elaboration of urine which is hypertonic to plasma is uniquely characteristic of the action of vasopressin. This suggests that chlorpropamide may act by enhancing the neurohypophyseal secretion of vasopressin, much as it enhances pancreatic islet-cell secretion of insulin. Pharmacologic stimulation of vasopressin release in man, independent of plasma osmolality, by means of nicotine, provides a physiologic precedent for this possibility.¹⁶ Moreover, this theory is in keeping with chlorpropamide's lack of effect in nephrogenic diabetes insipidus,^{1,5} wherein vaso-

*The antidiuretic action of aminopyrine was reported by B. S. Kahn in 1933 (JAMA 100:1593) but the drug received scant clinical application because of its potential hematologic toxicity.

ACTIVATES GENERATES PROMOTES
 VASOPRESSIN → ADENYL CYCLASE → CYCLIC AMP → WATER TRANSPORT

ATP → ADENYL CYCLASE → CYCLIC AMP → PHOSPHODIESTERASE → AMP

Chart 5.—Generally accepted sequence of vasopressin-induced water transport. (Possible role of chlorpropamide is discussed in text.)

pressin resistance, but not deficiency, is the problem. Augmentation of endogenous vasopressin levels would be of no benefit here since exogenous vasopressin is without effect. Therefore, if chlorpropamide acts by increasing endogenous hormone secretion, it should be effective only in vasopressin-deficient diabetes insipidus and not in the vasopressin-resistant form. Indeed, this seems to be the case.¹ Substantiation of this theory requires direct measurement of plasma vasopressin which has not yet been reported in this setting.

Alternatively, chlorpropamide may have a direct vasopressin-like effect or may potentiate the effect of minute amounts of vasopressin which persist in diabetes insipidus. These possibilities were investigated by Ingelfinger and Hays,^{17,18} using the toad bladder. They found that although chlorpropamide alone had no effect on water movement, it did potentiate vasopressin-induced water transport. This could result either from activation of renal tubular adenylyl cyclase which generates cyclic adenosine monophosphate (AMP) from adenosine triphosphate (ATP) or from inhibition of the phosphodiesterase which degrades cyclic AMP (Chart 5). Cyclic AMP has been shown to be the chemical mediator of vasopressin's water transporting effect. Since chlorpropamide did not enhance cyclic AMP-induced water transport, the authors reasoned that it must act by increasing the sensitivity of renal tubular adenylyl cyclase to vasopressin.¹⁷

Our data is consistent with this explanation. Milder cases of diabetes insipidus were more sensitive to chlorpropamide and responded better to this form of treatment than the more severe cases. In other words, those with low levels of circulating vasopressin (partial diabetes insipidus¹⁹) were more likely to respond than those without any hormone at all. Webster and Bain⁵ made similar observations. As for patients with nephrogenic diabetes insipidus, the lack of antidiuretic effect would imply that they lack the chlorpropamide-sensitive reaction involving adenylyl cyclase. We are unaware of any data bearing on this point, however.

The long-term safety of chlorpropamide has been demonstrated by its use for over a decade in the treatment of diabetes mellitus. Physicians are familiar with its infrequent adverse reactions. Initial fears that it might worsen diabetes mellitus by causing premature islet-cell exhaustion have been dispelled by the finding that after long-term treatment serum insulin levels actually become lower in concert with lower glucose levels.²⁰

In our experience to date, the only hazard associated with chlorpropamide therapy of diabetes insipidus has been hypoglycemia. Some degree of hypoglycemia developed sooner or later in almost all of our patients on the potent 500 mg dosage. This is in contrast to the experience of Arduino et al¹ and Reforzo Membrives et al,³ whose patients seemed to resist the drug's hypoglycemic effect. In our patients, chlorpropamide was of practical value as an antidiuretic agent only in cases in which it was effective in the 125 to 375 mg dose range. Higher doses almost invariably caused hypoglycemia. This may be attributed partially to the fact that three of our patients were small children, and three had other associated endocrine deficiencies. Patients with pan-hypopituitarism, including corticotrophin and growth hormone deficiency, were particularly susceptible to this complication.

Hypoglycemia could usually be avoided, however, by restricting the dose to around 250 mg and when necessary by adding hydrochlorothiazide to the regimen. The effects of these two drugs were found to be additive (Charts 2 and 3). Hydrochlorothiazide, by virtue of its own antidiuretic action, reduces the need for large doses of chlorpropamide and also protects against hypoglycemia, probably by inhibiting insulin secretion.²¹ Fortunately, significant hypokalemia is not usually encountered with doses of only 50 mg of hydrochlorothiazide. Hence, the two in combination yield a highly desirable therapeutic result.

Addendum

Since this manuscript was submitted for publication, Robertson and Mahr have shown (program of the Fifty-third Meeting of the Endocrine Society, 1971) by means of a highly sensitive radioimmunoassay that in patients with diabetes insipidus chlorpropamide does not increase plasma vasopressin levels. Their data indicates that the

antidiuresis results from augmentation of the antidiuretic effects of suboptimal amounts of vasopressin measurable in their patients.

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ADVANCES IN PLACENTAL FUNCTION TESTS

"The last five years have seen tremendous advances in the development of placental function tests. With the aid of several new procedures, the obstetrician is now able to assess the health of the unborn child. Anderson, in a report from the University of Southern California, delineates his experience with the determination of urinary estriol in the diabetic pregnancy. Although use of the quantitative chemical assay of the 24-hour urine specimen has been controversial and opinion divided as to its value, Anderson showed that he could reduce the perinatal mortality in the insulin-dependent diabetic from 17 percent when the estriol was not employed to 8 percent if it were employed to manage the time of delivery in these pregnancies. . . .

"Another significant report on placental function tests was that of Spellacy and associate from the University of Miami who have developed a test for human placental lactogen and employ this to assess the high-risk pregnancy. The greatest value of this test has been in the hypertensive complications of pregnancy. There is a 95 percent reduction in the human placental lactogen in the serum when the fetus is dying or in impending jeopardy. So this is a very important advance. As this test is developed, I am sure we will see almost routine employment of this material in the high-risk pregnancy."

—JOHN W. GREENE, JR., M.D., Lexington
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Triamcinolone-Procaïne in the Treatment of Zoster and Postzoster Neuralgia

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■ *Twenty-four patients with herpes zoster were treated with injections of 2 percent procaine hydrochloride containing 2 mg of triamcinolone per ml. The treatments were given subcutaneously under the cutaneous lesions and in areas of pain. The results were excellent in 22 patients. There was one failure—postzoster neuralgia in an 82-year-old woman.*

Of 12 patients with postherpetic neuralgia, eight had improvement of 70 to 90 percent and three had complete relief.

There were no significant complications in either group.

MANY INVESTIGATORS HAVE used many agents in the treatment of herpes zoster but the therapeutic efficacy of any of them is difficult to judge, for the disease is both self-limited and unpredictable. In 1957, Epstein and Allington¹ observed that no treatment advanced to that date was beneficial. None has been reported since that offers any greater hope. Now, a preliminary communication² having stirred a great deal of interest, I am reporting good results in 22 of 24 patients with herpes zoster who were treated with triamcinolone in procaine. And the use of this preparation in 12 cases of postzoster neuralgia (which is less apt to subside spontaneously) has given brilliant, but not invariable, results.

Technique of Treatment

The treatment, which can be done in the office, consists of subcutaneous injections of a solution containing 200 mg of triamcinolone in the form of Aristocort 40® or Aristospan® or Kena-

log® in 100 ml of 2 percent procaine hydrochloride. In some instances, saline solution or lidocaine (Xylocaine®) was substituted for the procaine hydrochloride. As the results with all three diluents and all three corticosteroid preparations were comparable one to another, the triamcinolone is believed to be the important factor in this treatment. The indicated amount of this mixture is injected *subcutaneously* beneath the visible lesions and into the areas of pain, burning or itching. The strength of the solution is 2 mg of triamcinolone per ml. Up to 20 ml of the solution can be injected along the involved segment during a single session. More than this amount may cause vertigo. This dosage has been used on the face as well as on the trunk and extremities. Repeated daily injections may be given until adequate relief has been obtained. No attempt is made to inject the solution into a nerve, or to administer it perineurally.

The reason for subcutaneous injection is to minimize the hazard of cutaneous atrophy which might add to the scarring caused by zoster in some patients. Moreover, care must be taken to avoid injecting the mixture into the adipose tis-

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sue lest painful panniculitis and abscess formation result. Maximum therapeutic benefits cannot be expected unless all of the involved areas are injected and it is important also that the dosage be adequate. For example, in one patient the initial dose was 15 ml (30 mg of triamcinolone) injected into the right side of the face. This was followed on successive days by injections into the same general area of 5 ml (10 mg), 3 ml (6 mg) and 5 ml (10 mg), a total of 28 ml (56 mg). Commonly 20 ml (40 mg) is injected daily into more extensive lesions on the trunk or limbs. Most patients respond well to smaller volumes of the mixture. The dose should be determined by the extent of involvement.

Often when the patient notices little or no lessening of discomfort after the first treatment, the reason is that the entire area was not anesthetized. This is an indication for further therapy. If the remaining areas of maximum discomfort are injected, beneficial results may be expected. The patients are instructed to note the locations of greatest pain and burning, and these are injected selectively in subsequent treatments.

Complications

Pain. The injection tends to be painful despite the use of procaine or lidocaine. A 25 gauge needle is used routinely to minimize the discomfort of insertion but the medication itself causes moderate pain or burning or both. In general the sensation is no greater than that caused by the insertion of a local anesthetic into or under the skin before a surgical procedure.

Hemorrhage. Bruising of the skin occurs commonly after the injection. It is more pronounced than that usually seen after similar subcutaneous injections of other medication, and it is noted most frequently in elderly patients and in those with postzoster neuralgia. This is merely a cosmetic handicap; it is not cause for discontinuing nor does it diminish the success of therapy.

Abscess. A sterile abscess developed in one patient with supraorbital zoster over the forehead. The lesion was not particularly discomforting and it cleared quickly after incision and drainage. The zoster responded rapidly and completely to this approach.

Scarring. No scarring was attributed to these injections, though the appraisal is a difficult one to make in the circumstances because the infec-

tion itself commonly causes cicatricial alterations. However, neither the physician nor the patient in any instance felt that the therapy had contributed to these permanent changes. There were no gross alterations in the scarring in patients with postzoster neuralgia even after many injections of this solution.

Vertigo. This is common in elderly patients, especially in those receiving more than 15 or 20 ml of the medication in a single day. It is short-lived and does not contraindicate further injections.

Failures. Postzoster neuralgia developed in one 82-year-old Negro woman with an acute zoster of the right side of the face. This did not respond to further therapy. In most reported series the incidence of postzoster neuralgia is about 10 percent. The incidence in the present group was 4.1 percent.

Results

Herpes Zoster. There were 24 patients with herpes zoster. One had persistent postzoster neuralgia. There were no other failures, although one patient who had good improvement after three injections did not return and the result is therefore uncertain. The results in the remaining 22 patients (91.6 percent) were considered to be excellent—complete clearing of pain, paresthesias and cutaneous manifestations. Scarring or absence of it was not considered in evaluating treatment.

The series was not a particularly benign one. Several investigators^{3,4} have pointed out that postzoster neuralgia is more common in older patients, and in the present group of 22 patients with acute herpes zoster, 12 were more than 60 years of age and 17 were over 50. The usual ratio of men to women in large series is about 1:1, and although in the present one there were eight men and 16 women (1:2) this is not considered a significant factor.

Seventy-five percent of the patients received four or fewer injections. The maximum was 13 doses—that in the patient who had persistent postzoster neuralgia. The average was 3.8 injections. The total volume of solution varied from 2 ml to 95 ml in the course of therapy, the average being 35.1 ml.

Postzoster neuralgia. There were twelve pa-

TABLE 1.—*Patients with Herpes Zoster Treated with Triamcinolone-Procaïne Injections*

<i>Case</i>	<i>Age</i>	<i>Sex</i>	<i>Location</i>	<i>Duration</i>	<i>No.</i>	<i>Injections Volume</i>	<i>Results</i>
1	74	F	Left forehead	"Days"	1	1.5	Excellent
2	83	F	Left 12 thoracic	"Days"	2	8	Excellent
3	68	F	Left 5 thoracic	1 week	4	?	Excellent
4	64	F	Right side face	5 days	4	28	Excellent
5	15	F	Right thigh	2 weeks	2	10	Excellent
6	71	F	Left 12 thoracic	1 week	1	5	Excellent
7	72	M	Left 10, 11, 12 thoracic	2 days	4	40	Excellent
8	63	F	Left 10 thoracic	2 weeks	3	40	Excellent
9	48	M	Right 12 thoracic	2 days	6	60	Excellent
10	71	F	Right 12 thoracic	2 weeks	6	70	Excellent
11	69	F	Left neck, arm	1 week	7	20	Excellent
12	51	M	Left forehead, nose, eyelids	4 days	4	33	Excellent
13	64	F	Left 12 thoracic	2 weeks	3	30	Improved, stopped treatment
14	22	F	Left 12 thoracic	1 week	7	95	Excellent
15	21	M	Left scalp	1 week	2	2	Excellent
16	67	F	Left 1st lumbar	2 days	6	60	Excellent
17	36	M	Left ophthalmic	9 days	1	10	Excellent
18	29	M	Right neck, chest, shoulder, back	1 week	3	45	Excellent
19	82	F	Right cheek, lip	1 week	13	91	Residual neuralgia
20	71	F	Left thigh, back	6 days	3	45	Excellent
21	58	M	Left neck, chest, shoulder	4 days	3	30	Excellent
22	60	F	Right eyelids, nose	2 weeks	1	5	Excellent
23	55	F	Right buttock	1 day	3	60	Excellent
24	31	M	Left axilla, back	6 days	2	20	Excellent

TABLE 2.—*Patients with Postzoster Neuralgia Treated with Triamcinolone-Procaïne Injections*

<i>No.</i>	<i>Age</i>	<i>Sex</i>	<i>Location</i>	<i>Duration</i>	<i>No.</i>	<i>Injections Volume</i>	<i>Results</i>
1	54	F	Right 11 thoracic	3 months	2	10	Excellent
2	56	F	Left hand, arm, back	14 months	3	15	90% well
3	47	F	Left 5 thoracic	2 months	6	18	95% well
4	94	M	Leg	3 months	2	10	90% well
5	65	F	Left 6 thoracic	11 years	3	25	90% well
6	72	F	Left 1, 2, 3 lumbar	2 years	4	?	95% well
7	18	M	Left 4 thoracic	7 months	1	5	Excellent
8	74	M	Left 12 thoracic	5½ years	30	430	Moderate improvement
9	67	M	Left 6 thoracic	1 month	15	290	Excellent
10	67	F	Left 12 thoracic	4 years	16	216½	90% well
11	73	F	Left 12 thoracic	3½ years	16	299	75% well
12	70	F	Left arm, hand	1 year	4	20	50% well

tients with postzoster neuralgia of one month's to 11 years' duration, the average being 27.7 months. Four were men, eight women. Eight were more than 60 years of age and ten were over 50. The number of injections ranged from one to thirty, the average being 8.5 per patient. The volume of solution varied from 5 to 430 ml and the average was 121.8 ml. Three of the 12 patients had complete abatement of symptoms (none of the three had had symptoms for longer

than seven months) and eight had improvement that, by the patients' appraisal, was from 70 per cent to more than 90 per cent (mild paresthesias persisting). In one case, listed as a treatment failure, the dosage was grossly inadequate—four injections of 5 ml each. The 11 patients who were benefited felt that the course of therapy was well worth the cost, the inconvenience and the discomfort of the injections.

Therefore, even in this very resistant disabling

complication of zoster, this therapy could be considered to be successful, even if not invariably so.

Discussion

The evidence thus far is that the treatment herein described is a valuable one in the treatment of herpes zoster and postzoster neuralgia. The series is reasonably large—24 patients with acute zoster, 12 with postinfection neuritis. The immediate results in the dermatosis stage were excellent. The course of the disease was not shortened (an average of 19.5 days) but the low incidence of postzoster neuralgia plus prompt alleviation of discomfort indicates that the treatment is worthwhile. Eaglstein and coworkers⁴ found that systemic corticosteroids did not shorten the course of the infection but did relieve pain and decrease the likelihood of persistent pain. The injections used in the present series did the same but in a higher proportion of patients. In the Eaglstein series, 30 percent of the treated patients had postherpetic neuralgia (persistence of pain for more than eight weeks) and the pain was not alleviated until the patients had received at least two weeks of oral therapy with triamcinolone.

The use of intralesional corticosteroid injections would seem to be a reasonable therapeutic measure in herpes zoster since probably neural and perineural inflammation are important in the development of symptoms. Sehgal and Gardner treated 12 patients with postzoster neuralgia by the local injection of hydrocortisone and procaine and reported results "good" in two and "fair" in five, and "poor" in three patients who were treated by local injection of procaine alone.⁵ These investigators also treated 12 patients with vitamin B₁₂ (the results in all were poor), dilantin (14 out of 15 poor), cortisone by mouth (poor in all six patients followed), epidural injection of procaine and hydrocortisone acetate (eight poor results, two fair), and the intradural injection of methyl prednisolone acetate (18 poor, two fair). So, in their series, the best results were obtained by the local injection of a corticosteroid and a local anesthetic. Had triamcinolone been used, as in the series here reported, the results might have been better than those obtained with hydrocortisone.

It is in the treatment of postzoster neuralgia

that the method here described appears to be of greatest use. This condition is not self-limited. It seldom subsides spontaneously after it has been present for as long as a year. In seven of the group of 12 postzoster neuralgia patients herein reported, the pain had persisted for a year. Yet in nine of the group the benefit was rated at more than 70 percent and to 90 percent or more. Considering the therapeutic resistance of this manifestation, one must recognize the value of this procedure though acknowledging that it does not eradicate all the symptoms in all patients. It must be stressed that adequate dosage is essential although partial remission occurs promptly after a few injections in most cases.

There has been some fear that corticosteroids might cause dissemination of the viral infection. However, there is now sufficient evidence to establish that this is very rare if it occurs at all. No side effects were encountered in this series.

There is a certain amount of evidence that the procaine is not the crucial ingredient in this therapy. In one patient saline solution was substituted for the local anesthetic and the result was still good. In another, both triamcinolone and procaine were used separately without benefit. Procaine alone was ineffective in three instances reported by Sehgal and Gardner.⁵ However, it is recognized that local anesthetic agents alone have a dramatic result in some cases. Regardless of whether the beneficial effects are from the corticosteroid or the local anesthetic or the combination, it is of practical importance that the combination has proved successful in these patients with zoster or postherpetic neuralgia.

It should be stressed that while occasionally all symptoms may abate after the first injection, in most cases repeated injections are necessary. It is important that the physician identify the points of maximum discomfort as accurately as possible and administer the medication selectively into these areas. Extensive eruptions can be controlled by this technique.

There were no controls for comparison in this study, the treatment having been used regularly after it gave relief to the first patient on whom it was tried. In some cases, however, attempts were made to inject one portion of a lesion with the active principle and others with saline solution alone. Where that was done, patients denied noting any improvement. It is believed that there is too much overlapping of nerve fibers to permit

clearcut distinction between the treated and the placebo-injected areas. Furthermore, the pain sensation is not localized clearly enough to allow the patient to distinguish smaller asymptomatic areas within a painful lesion. One patient did offer a control of sorts. He had a severe zoster of the trunk with intra-abdominal pain. With the injection treatment the cutaneous lesions and symptoms cleared quickly, but the visceral symptoms have persisted for more than two years.

Comparison with other reported series makes it obvious that the treatment described is also effective in postzoster neuralgia.

ADDENDUM. After the foregoing report was written, normal saline solution was substituted for procaine as a diluent. No change was made in the dosage or form of the triamcinolone. Fourteen more patients were treated by this combination of Aristospan in saline solution, making a total of 50 patients treated. Three had postzoster neuralgia. In one patient there was complete alleviation of symptoms. In another, the results were "good" and in the third, the benefits obtained were considered "fair." Nine of the 11 patients with acute zoster had prompt and complete clearing. One did not return for further

therapy or observation after the first injection. In one, postherpetic neuralgia persisted. This patient, who was decidedly senile, produced severe excoriations in the involved area. She was treated also with triamcinolone in procaine without effect. Therefore, one can conclude that the procaine is not a factor in the results obtained. However, this change in the diluent eliminated the vertigo mentioned previously. An abscess in the injected area on the trunk developed in one patient of this additional group.

TRADE AND GENERIC NAMES OF DRUGS

<i>Aristocort</i> ®triamcinolone
<i>Aristospan</i> ®triamcinolone
<i>Kenalog</i> ®triamcinolone
<i>Xylocaine</i> ®lidocaine

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DIAGNOSIS OF HASHIMOTO'S THYROIDITIS

"If Hashimoto's thyroiditis is suspected . . . we frequently will do a needle biopsy of the gland as an office procedure and in so doing the pathology can be established. If substantiated, the treatment is thyroid replacement medication. However, if this is the diagnosis and if the gland is treated medically, close observation is extremely important for six to twelve months because in 3 percent of our patients who were treated surgically (18 of 605) papillary cancers were found. Also lymphosarcoma is seen to coexist in the presence of Hashimoto's thyroiditis, again in approximately 3 percent of cases. So if the goiter does not disappear under medical management over a period of three to six months or if there's any evidence of increase in size of the gland during this period of time, then it becomes extremely important that the goiter be removed surgically to rule out significant pathology other than that which is suspected."

—OLIVER H. BEAHR, M.D., Rochester
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Childhood Encopresis

A Neurodevelopmental-Family Approach to Management

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CHILDHOOD ENCOPIRESIS, although not rare, is given little notice in the pediatric and surgical literature, where it is known as "functional megacolon" or "chronic obstipation with fecal soiling." The problem usually reaches the attention of a physician after the symptoms can no longer be obscured and are presented as a mass in the abdomen (fecalith with megacolon, to be differentiated from aganglionic megacolon¹) or after an "accident" of fecal soiling has occurred away from home. With fear of exposure, the "potting couple"² (mother and child) attempt to keep these symptoms concealed, with increasing anxiety and heightened parent-child conflict. Usually the child has been shamed and the parents fear their secret will become known outside the family to friends or to the pediatrician.

Richmond³ has three classifications of megacolon: (1) psychogenic, (2) neurogenic (Hirschsprung's disease), and (3) anatomic. Richmond and Huschka^{3,4} subscribe to the belief that fecal soiling is psychogenic, the most popular view up to this time.

Anthony reviewed the many facets that contribute to this behavior complex in his classic study in 1957^{5,6}. He discussed the psychodynamics, the different cultural patterns, the taboos of bowel training, and the differences of family style of bowel training. He also described the kinds of mothers, the socio-economic style of toilet training, the kinds of mother-child relationships,

the association of encopresis with enuresis, and various etiologic problems. While the kinds of mothers are discussed, little is said about the kinds of children in whom this problem is found. Anthony outlined two categories of encopresis based on the kind of mother: one coercive, strict, clean; the other non-coercive, lenient, dirty.

The purpose of this article is to present a neurodevelopmental-family approach to the psychopathology of childhood encopresis—another dimension in the understanding, origin and management of this problem (see chart). The discussion will be confined, however, to the important issue of the child's neurodevelopmental state as a possible factor in the cause and in the management of this problem. In keeping with popular myth, traditional psychiatric management has focused primarily upon the maternal-child relationship, with little attention given to the child's neurodevelopmental state in response to the family system. It is true that the mother's personality in toilet training practices contributes significantly to the mother-child conflict; but attention should also be given to the kinds of children in whom this problem is so frequently, though not exclusively, associated and the kind of neurodevelopmental state the child brings to the living situation.

Definition of Encopresis

The term *encopresis* will be confined to the problems of holding back of feces or retention of feces with or without fecal soiling, associated with maternal-child conflict. In this disorder the manner and place of defecation differs from child to child, occurring usually in a place other than the toilet—under the piano, in the backyard, in a

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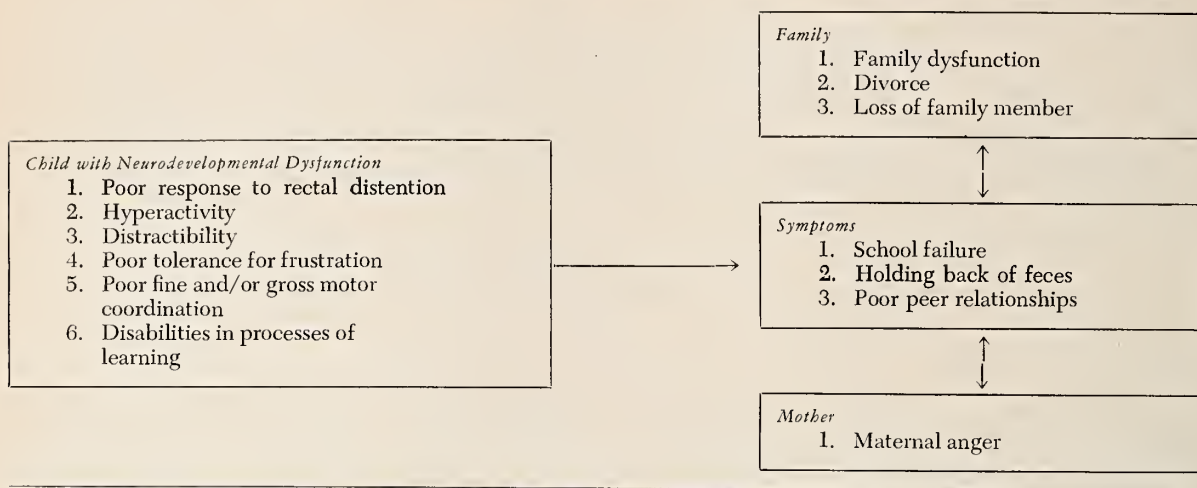
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*Anthony's article² is one of three articles^{5,6} listed in the Index Medicus since 1956 under the title "encopresis."

ISSUES INVOLVED IN THE ETIOLOGY OF ENCOPIRESIS
(Theoretical Model)



closet, while the child plays alone in a squatting position—and only at home, not at school, which indicates the child's own preference for a "special" place to have a bowel movement.

The problem of encopresis is not uncommon in my practice, which is limited to childhood learning and behavior problems, and it appears to occur with a greater frequency in boys than girls. It is often one of several concomitant symptom complexes not infrequently associated with a group of children with neurodevelopmental learning and behavior problems, which also are known to occur more frequently in boys than girls. Although many children are referred with the primary complaint of encopresis, in the majority of patients with this problem it is identified only incidentally, often months after treatment is in process for some other reason.

Description of Toilet Training

The newborn infant and child within the first year and a half of life automatically empties his bowel or bladder in response to distension. During the period of toilet training—nine months to three years of age—the automatic, involuntary process soon becomes a voluntary act associated with morality and taboos. It is during this period that the bowel and bladder are invested with strong ideas of goodness and badness constituting what Anthony calls "sphincter morality." Attitudes such as disgust ensuing from this system become inseparable from the alimentary tract and are localized in common speech somewhere

along the course. The youngster is "good" when he has either indicated a need to go to the bathroom or when he can independently take care of his own needs. He soon learns to avoid discussion of this topic in public altogether.

Natural History of Encopresis

The symptoms of holding back may appear before the serious maternal-child conflict develops. For reasons not completely clear the child holds back feces, which accumulate, become hard, and eventually are very painful to pass. One explanation may be that the youngster does not readily experience the discomfort of rectal distension. In any case, conflict arises when the symptoms arouse fear and anger in the mother and are used by the child in a power struggle to control and enjoy secondary gains from these symptoms. Such a child has a greater need to control, since he has less than ordinary self-assurance in general and the intensity of the conflict depends on the extent to which the mother's self-esteem is threatened by the symptoms. She fears blame for this "socially unacceptable" problem. In addition, when the child continues to have symptoms, the mother expresses helplessness and anger resulting from loss of parental authority and control. The problem is often sustained when the conflict and symptoms begin to serve a function to maintain homeostasis in a dysfunctional family. The symptoms keep the child from functioning outside of the family at school, at camp or with friends. The child is implicitly encouraged

by both parents on a covert level to become the family scapegoat. The myth that "everything would be fine if it weren't for Billy's problems" channels tension from serious problems the parents experience with and between themselves.⁷

Task Analysis

Early in the toilet training experience, before expressive language and good motor coordination of the hands develop, when the child has a short attention span and frustrates easily, the parents actively participate with the child in toilet training. They answer to the child's sounds, signals and expressions that indicate his need to go to the bathroom. At this time the mother or father, as the case may be, assists the small infant and child by opening the bathroom door (as the knob is out of his reach) and by undressing the child (which he may be unable to do by himself). For voluntary bowel evacuation, the infant and small child needs to respond to a sensation of rectal distension and fullness. For the older child to have a bowel movement, he must be able to experience and respond to the physiological signal of rectal distension, have good coordination of the hands to open the door and undress himself, have the ability to overcome fear of heights on the toilet seat, and be able to tolerate the frustration of having to interrupt play with others (an even more intolerable situation if the youngster has trouble "holding onto friends"). Finally, he must have a good span of attention so that he may be able to sit long enough to accomplish this task in the absence of distractibility and hyperactivity.

If, during the critical time of toilet training—nine months to three years of age—the child is hyperactive and distractible, with poor coordination of the hands, who frustrates easily, fails to experience discomfort from rectal distension at the usual threshold, and anticipates and expects pain when large accumulations of feces are finally passed, he is more likely to develop symptoms of encopresis than the youngster without these problems. These hyperactive, distractible, poorly coordinated, "immature" children with poor tolerance for frustration have many sources of anger and frustration resulting from poor relationships with peers and parents and school failure. These children are generally very difficult to handle. Since they have few avenues for success, control, or competency in any one area, these children

are usually angry and unhappy with a great need to control when mother brings toilet training into the "arena." This might explain why these same children are often poor eaters and have symptoms of enuresis.

By the time an eight or nine-year-old youngster with encopresis is seen by a physician, the mother and child have experienced a whole range of feelings. The embarrassed child with the symptoms has aroused angry feelings in his mother. The mother at some time has used threats, bribes, shame, enemas, laxatives, and spankings. She is seen by the child as a frightened, angry person with "weapons" (enema bags, laxatives, suppositories) determined to remove the obstruction, while the youngster stubbornly tries to stay in control of himself by saying in effect, "This is my bowel and I'll control what goes in and what goes out."

The Study

In the five cases that will be outlined, all the children were boys with demonstrable evidence of neurodevelopmental dysfunction. One child was referred with the chief complaint of encopresis and bowel obstruction and after evaluation was found to have a specific learning disorder (an expression of neurodevelopmental dysfunction). The other four were referred for evaluation of reading problems and later were found to have the problem of encopresis.

All five children were between the ages of five and a half and twelve years with testing scores which fell within the "normal, average" range of intelligence on the Wechsler Intelligence Scale for Children (wisc). As noted in Table 1, these five boys had significant delays in the development of written and spoken language skills, that is, reading, spelling or arithmetic, and were hyperactive, distractible, easily frustrated or inattentive. All had specific learning disabilities. That is, they had normal intelligence with disabilities in one or more processes of learning that interfered with normal acquisition of written or spoken language skills.⁸ Neurological examination demonstrated findings consistent with the diagnosis of neurodevelopmental dysfunction including difficulty with fine motor coordination of the hands, dyspraxia of the upper and lower extremities, marked synkinesia, and difficulties with balance. There was no consistent pattern in maternal style (clean-strict versus dirty-lenient),

TABLE 1.—Data on Patients and Ambience in Five Cases of Childhood Encopresis

	Case 1	Case 2	Case 3	Case 4	Case 5
Age	9 years 0 months	5 years 7 months	10 years 3 months	12 years 11 months	9 years 3 months
Reason for Referral	Reading & behavior problems	Bowel obstruction	Reading problems	Reading problem	Reading problem
School Grade	2nd (Repeating)	Kindergarten	4th	6th	3rd
Achievement Levels					
Arithmetic	2nd to 4th	Prekindergarten	4th	2nd	2.5
Spelling	Below 1st	Prekindergarten	3rd	2nd	2.8
Reading	1st	Prekindergarten	3rd	2nd	2.5
WISC Scores					
Verbal IQ	101	101	90	101	104
Performance IQ	94	107	120	101	101
Full Scale IQ	98	104	109	101	103
Disabled Processes of Learning	Visual memory for forms & visual-motor integration	Visual memory for forms, visual sequential memory, & visual-motor integration	Auditory & visual short-term sequential memory & poor expressive language	Visual memory for forms, auditory & visual sequencing, & visual-motor integration	Visual-motor integration & visual sequencing
Onset of Language Development	Delayed	Early & good	Delayed	Delayed	Early & good
Neurological Findings	Dyspraxic gait, poor rapid alternating & finger-thumb movements, & synkinesia	Disturbed balance, fine motor hand incoordination, & dyspraxia of upper & lower extremities	Poor fine coordination of hands & dyspraxia of upper & lower extremities	Right-left confusion & poor fine motor hand coordination	Poor rapid alternating movements & fine motor incoordination
Neurophysiological State	Infantile voice, hyperactive, poor frustration tolerance, & poor impulse control	Hyperactive, short attention span, & distractible with good impulse control	Poor frustration tolerance, distractible, hyperactive & impulsive	Immature, nonaggressive with good frustration tolerance, hyperactive	Frustrates easily, "immature," short attention span & distractible
Emotional Behavior	Immature, fearful of making mistakes, negative, foolish & inappropriate behavior	Worries, separation anxiety, difficulty in expressing feelings, fearful of mistakes, poor appetite	Poor social judgment & peer relationships; tearful & sad	Listless, apathetic, denies feelings, worried smile, clowns, desperate, despairs, never complains	Nervous talker, poor peer relationships, lonely, likes fearful carnival rides, poor appetite hyperactive
Onset of Toilet Training	Early	Early	Late	Late	Late
Kind of Family	Dysfunctional	Dysfunctional	Dysfunctional	Functional	Functional
Significant Family Members	<i>Mother:</i> Business school, intelligent, clean, disorganized, poor self-esteem, unable to set limits, good-natured, & anxiety-ridden <i>Father:</i> Uninvolved <i>Paternal Grandmother:</i> Critical	<i>Mother:</i> Divorced, high school grad., intelligent, "cold," "chip on shoulder," resentful, rebellious <i>Father:</i> Loving	<i>Mother:</i> Educated (BA), intelligent, clean, divorced, lonely, loving, indulgent, defenseless & good-natured <i>Father:</i> Critical <i>Maternal Uncle:</i> Critical	<i>Mother:</i> Intelligent (BA), clean, robust, good-natured, avoids reality, permissive <i>Father:</i> Quiet & serious	<i>Mother:</i> Intelligent (BA), clean, elegant, self-confident <i>Father:</i> Loving <i>Other:</i> Patient raised by indulgent, over-protective "Nanny."

family education, economic and marital status, or onset of the child's toilet training. Two of the families could be considered functional. Of the three dysfunctional families, two were broken homes where the child experienced the loss of a significant adult. In the intact dysfunctional family, each parent had serious and significant intrapersonal problems which placed the handicapped youngster in an outrageous position as the family scapegoat.

The treatment of the five children in this study was directed toward management of the processes, not toward the symptom itself, so that continued use of enemas and laxatives was carefully avoided and the child was protected against unnecessary traumatic diagnostic procedures. Therapy was directed toward the basic problems of neurodevelopmental dysfunction and family dysfunction that contributed to the child's anger and frustration.

In each of the five cases the following approach to treatment was used:

Diagnostic Evaluation: The youngsters referred with the primary symptom of encopresis as well as those with school and learning problems were seen in a family interview followed by a developmental assessment by a psychologist, an educational evaluation by a teacher, a speech and language evaluation by a speech and language pathologist, hearing and vision tests, and a summary and planning conference with the parents. The developmental assessment included the wisc, the Developmental Test of Visual-Motor Integration, the Illinois Test of Psycholinguistic Abilities, the Bender Visual-Motor Gestalt Test, the Frostig Developmental Test of Visual Perception, the Spencer Memory Test, and the Peabody Picture Vocabulary Test. The educational evaluation included the Durrell Analysis of Reading Difficulty, the Monroe Reading Aptitude Test, and the Gates-McKillop Reading Diagnostic Test. During the developmental assessment and educational evaluation the child's achievement in learned skills and specific processes of learning were studied including an evaluation of his sensory perceptual integration, neuro-motor development, concepts of spatial relationships, body image, auditory and visual skills, and ability to use symbols, understand language and form concepts. Symptoms and signs of emotional stress were also observed.

Medication⁹: All five boys responded to a trial

of Ritalin[®] (methylphenidate hydrochloride) 5 to 10 mg twice a day for symptoms of hyperactivity, distractibility, short attention span, etc. Dexedrine[®] (dextroamphetamine sulfate) 2.5 to 5 mg or Librium[®] (chlordiazepoxide hydrochloride) 5 to 10 mg is often effective when the desired response to Ritalin was not achieved.

Academic Program: Each boy demonstrated significant delays in acquiring one or more language skills (reading, spelling, writing, speaking, arithmetic). With special tutorial help on a one-to-one basis or various special class placements, the boys began to feel more successful at school and at home, and developed improved mastery of skills which greatly lessened their frustration and anger.

Family Therapy: An attempt was made to follow each child in Family Therapy (not individual therapy for the child), to improve the parents' understanding of the problems and give them a clearer identification of the issues, roles, feelings and values to permit change within the family system. The parents were encouraged to open expression of their feelings. In each case the parents were assisted in removing the symptoms from a power struggle with the child since the mothers often gave additional power to the child by saying, "You're doing this to hurt me." When this occurred, the parents were directed to say, "You're not having a bowel movement for me but for yourself." The children were allowed to assume responsibility for themselves by getting to the toilet regularly and being in charge of their own dirty clothes.

Appropriate Diet: A large fluid intake, fresh fruit and vegetables were encouraged. Constipating foods, such as rice, apples, milk and milk products were avoided. In the beginning, the use of a stool softener, Metamucil[®], one packet three times a day was recommended.

Reports of Cases

Two of the five cases will be presented. In the first case the child was referred for evaluation of learning and behavior problems and was found on evaluation to have the problem of encopresis. The second was referred with the diagnosis of encopresis following acute bowel obstruction and negative rectal biopsy and was found on evaluation to have neurodevelopmental learning and behavior problems.

Case 1. A 9-year-old boy repeated the second

grade and was referred for evaluation of learning and behavior problems. The parents and teachers complained about his hyperactivity, impulsivity, poor tolerance for frustration, and inability to read. Although his symptoms of encopresis were of major concern to the parents, they sought help for his learning and management problems and only casually mentioned on the third or fourth visit the problem of daily, afterschool fecal soiling. Teachers complained of his odor and children avoided him. His stools were enormous and infrequently passed, never into the toilet. He took no responsibility for his bathroom activities and the mother was beside herself, embarrassed, ashamed, and angry. She had tried bribery, shame, coercion, and avoidance—with failure in all efforts.

The patient was one of two children from the current marriage. The mother had a teen-aged daughter born out of wedlock from a previous marriage. The father was a stutterer, had never achieved financial independence and lived with his family on his mother's estate. His wife assumed all the responsibility for the children's care. She had had such a depressed and limited childhood herself that she felt lucky to have a roof over her head. She made excuses for her husband's immaturity and inability to achieve. She felt beholden to her husband and mother-in-law for her existence, feeling lucky since this was the best she could do for herself.

The mother had pronounced difficulty in expressing her feelings and tended to rationalize and pretend things were all right. The more she denied her feelings of resentment, the more harassed and disorganized she became. She spoke rapidly under pressure with a flushed face and hyperventilation. The patient's behavior and learning problems were a constant threat to her self-esteem. Her unsuccessful task of handling him all by herself was further undermined by the father's continued double-level messages—he gave lip service to his concern on the one hand and laughed and encouraged the boy's inappropriate behavior on the other.

The patient had been born (birth weight 8 pounds 4 ounces) following a pregnancy complicated by edema in the last trimester and Preludin medication for weight reduction throughout the pregnancy. Neonatal diarrhea responded to soybean preparation. He was an easy, placid baby and walked at nine months, after which

time the parents had difficulty keeping him within an enclosure.

Toilet training was started at nine months on the insistence of the paternal grandmother. There was considerable conflict between the mother and mother-in-law around this issue. According to the mother, the patient was never successfully toilet trained and "seems to hold it for me," since accidents seldom occurred at school but generally at home.

Language development was slow in onset and the patient was not speaking in sentences until three years of age. At the time of the evaluation, his voice quality was infantile and high-pitched and he showed immature grammatical usage forms.

From the early toddler stage to the present time, he has been hyperactive, with purposeless movements. He is easily distracted in school and tolerates frustration poorly. In the office he initiated foolish behavior which became self-stimulating and difficult to control. During these times the father laughed at the foolishness and the mother appeared helpless with anxiety.

The patient is a handsome, blonde boy in the upper 90th percentile for height and weight. His facial expression and bodily contour look like those of a younger child magnified in size. He enters the room like a steamroller; the walls literally shake.

During the first interview, he constantly tested limits and showed no social appropriateness as he experimented with different types of behavior. He became extremely self-conscious when school was discussed. He became foolish and crawled on the floor like a baby, assumed very infantile speech and behavior, sucked his fingers, threw his head back and made wincing facial expressions. He had difficulty setting his own limits. The mother had mounting anxiety and helplessness as she seemed to share the greatest burden while the father offered little support and took the whole problem lightly.

General physical examination was essentially negative. The neurological examination was significant. The findings of striate movements of the face, pronounced synkinesia, dyspraxic gait, poor finger-thumb movements, difficulty with rapid alternating movements of the hands, and rostral dominance were consistent with a diagnosis of neurodevelopmental dysfunction.

On psychological testing he functioned in

the area of "normal, average" intelligence. His strengths lay in his quickness to analyze problems and his excellent common sense in analyzing social tasks in the picture stories, both verbally and non-verbally. In addition, he showed an unusually high ability to concentrate on digit repetition, where he performed considerably above his age level. He showed difficulty with figure-ground discrimination and visual-motor coordination where he performed at a six-year nine-month level on the Frostig Eye-Motor Coordination Test, at a six-year level on the Developmental Test of Visual-Motor Integration, and at an eight-year level on the Bender-Gestalt Test which is a test of visual-motor integration.

The educational evaluation included the Durrell Analysis of Reading Difficulty, the Monroe Reading Aptitude Test, and the Gates-McKillop Reading Diagnostic Test. Silent reading comprehension was at the grade 1 level and oral reading comprehension of grade 2 material was good. His spelling was below first grade.

At the close of the evaluation administration of Ritalin was begun, 10 mg twice a day, with dramatic improvement in hyperactivity and impulsivity. He entered a one-to-one tutorial program with a reading expert and was placed in a disability class for the educationally handicapped, where he went from the first to second grade in reading in six months.

The patient and his parents were seen together in family therapy at two-week intervals. After several months, various family members continued to come in without the father for a one-year period. Dramatic improvement occurred during the first six months. However, a gradual deterioration of the patient's problems occurred once the father dropped from therapy and the patient stopped going to the tutor.

At last report the mother's teen-aged daughter had had a pregnancy aborted. She left home following overt sexual advances by her stepfather, who had been harsh and critical of her "morals." The mother had become increasingly more distraught and confused. She felt betrayed by her daughter and, tragically, for the first time enjoyed the position of advantage over her husband. She was drinking heavily and the patient's problems were reported by the school as serious.

Case 2. The patient was a five-and-a-half-year-old boy whose parents had been divorced since he was two years old. He lived with his young

mother in a small apartment and stayed with a babysitter during the day when not in school. The mother was extremely upset with the thought of giving up her job should the sitter become less tolerant of the boy's fecal soiling. Two weeks before he was referred by the mother's internist, the patient was hospitalized by his own general practitioner for fecal impaction. A consultant ruled out congenital Hirschsprung's disease by rectal biopsy and proctological examination.

The patient's father, a student in oceanography, who lived with his divorced wife's mother brought him in for most of the office visits. Both parents were present, however, for the summary and planning interview.

His mother was 19 at the time of his birth (birth weight 9 pounds) which followed a normal pregnancy and delivery. There were no early feeding problems and the baby gained weight normally. He was sitting and walking at the usual times. Rectal bleeding occurred at 19 months, presumably from a rectal polyp.

Language development aroused no concern in the parents and his speech was readily understandable to outsiders by the time he entered kindergarten.

Toilet training began "early." The patient developed night time control of urine quite early but "never really gained bowel control." His parents reported that at the age of four years he had bowel movements in his pants because "he was too busy to stop playing." When symptoms of fecal soiling associated with loss of appetite began at age five, his mother forced him to eat. The boy had difficulty expressing his feelings and was angry when his mother left him at the sitter's home.

General physical examination showed frontal prominence and deeply set eyes which gave him a gaunt appearance. The findings of the pediatric neurological examination of poor fine and gross motor coordination of the hands, hyperactivity, distractibility, striate movements of the face and posturing movements of the body on arm extension test, poor finger-thumb movements, poor rapid alternating movements, difficulty with balance, hyperactive deep tendon reflexes, were consistent with a diagnosis of neurodevelopmental dysfunction.

On psychological testing he had a full scale intelligence quotient on the WISC of 104, verbal IQ

101, and performance IQ 107—at least average general intelligence. Language skills seemed to be quite good and concept formations appeared adequate. Both hyperactivity and emotional reaction to potentially difficult tasks interfered with task performance. He demonstrated great difficulty in tasks requiring fine visual-motor coordination. On the Beery-Buktenika Visual-Motor Integration Test his age equivalence was four years nine months.

The patient worried about separating from his mother and demonstrated this by not wanting to go to school in the morning. When away from his mother he feared she might be harmed and not return. He had great difficulty in showing his feelings and was very fearful of making mistakes. In spite of his hyperactivity, inattentiveness and distractibility, he was considered to be a model child at school, which must have required remarkable control.

The response to Ritalin, 5 mg twice a day, given for his hyperactivity, was good. The findings were explained to both parents and the boy was referred to the University of California, San Francisco, Reading and Language Development Clinic to help him with his visual-motor integration problems. The mother was encouraged to have him express his feelings more openly and instructed that he was not to be forced to eat. The patient was started on a diet free of milk products, apples, and rice (which are in themselves constipating). Enemas were discontinued and the parents were encouraged to use Metamucil, 1 packet 3 times a day, until regular bowel pattern could be established. Soon after the evaluation, the boy went to live with his paternal grandmother and did not return for follow-up.

Conclusion and Summary

Childhood encopresis can be viewed as a complicated symptom complex. It is not rare and is often presented as an incidental finding due to its social stigma. It occurs most frequently in boys and is not uncommonly associated in my experience with a group of children found or known to have neurodevelopmental learning and behavior problems. When the primary complaint

presents as encopresis, this association should alert the physician to the possible presence of neurodevelopmental dysfunction. Knowledge of this association can improve understanding and management. One should avoid unnecessary assault upon these children with fearsome diagnostic procedures.

The problem does not appear as the result of a single variable—as the result of maternal-child conflict. This traditional simplistic theory blames the mother and ignores the child's neurodevelopmental state in response to the family system. In the five cases reviewed no specific kind of mother (strict, coercive, clean versus lenient, non-coercive, dirty) was found, but rather a specific kind of child in whom the problem of encopresis is commonly, though not exclusively, associated. Phenomenologically, the early symptoms of holding back may precede the serious maternal-child conflict which ensues. My own clinical experience with these children has led me to suggest that the neuro-physiological state of low frustration tolerance, distractibility, short attention span, variable hyperactivity, or learning problems with failure to respond to rectal distension may well determine the child's response to toilet training practices. Both child and mother are angered and frustrated by these problems, and conflict may be heightened and sustained when the symptoms begin to maintain the child as a scapegoat in a dysfunctional family. Treatment of these children was directed toward the problems related to the child's neuro-developmental state and family process rather than toward the symptom.

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Malaria

An "Imported" Disease to Be Reckoned with in the U.S.

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■ *Malaria is a treatable, potentially fatal disease. A detailed travel history and personal attention to laboratory diagnosis are essential. Infection related to current military ventures plus continued ever increasing civilian travel make it a disease to be borne in mind by medical practitioners.*

REMARKABLE ADVANCES in malariology have been made within our lifetime.^{1,2} These include the synthesis of drugs for treatment and prophylaxis, the discovery of residual insecticides, the institution of eradication programs, and the discovery of parasites and mosquitoes resistant to these measures. Despite intensive efforts, eradication programs have not even been started in parts of the world inhabited by 362 million people³ and 638 million live where malaria is still endemic.¹ Malaria remains the most prevalent of all diseases.

It is difficult to appreciate that malaria was endemic in the United States in the early 1900s, with four million cases annually, and perhaps one in twenty of them terminated fatally.⁴ In some southeastern states malaria was so common that schools had "chilling beds" for children with paroxysms of malaria. By the time the National Malaria Eradication Program in the United States was begun, in 1947, the disease incidence was already waning (Table 1). Today malaria is no longer endemic and most cases are imported.

Malaria can be classified according to its source (Table 2). More than 250,000 troops who had been in Korea at the time of the conflict there had clinical attacks of malaria after returning to the

United States. Despite the presence of appropriate vector mosquitoes in this country, only 85 secondary cases occurred.³ Thirty-five of these

TABLE 1.—*Malaria in the United States*

Year	Total Reported Cases*
Before 1935	>100,000
1947	50,000
1950	<2,500
1956	125
1957	103
1958	72
1959	54
1960	63
1961	85
1962	119
1963	148
1964	171
1965	156
1966	678
1967	2,855
1968	2,610

*Some of these figures are approximations, and others depend on whether or not patients symptomatic prior to arrival in the United States are included.

TABLE 2.—*Malaria Classified by Origin*

1. Imported
2. Not related to travel
 - a) endemic (indigenous)
 - b) introduced (secondary) (mosquito transmission from imported cases in area without endemic malaria)
 - c) induced (blood transfusions, common syringes)

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represented an epidemic in and around a summer camp in Lake Vera, Nevada County, California. These cases were traced to one veteran who slept outdoors during a relapse of vivax malaria.⁵ Current involvement in Southeast Asia has led to a second peak of imported cases, and isolated secondary cases have been reported over the past few years. In addition to military-related malaria, approximately two million United States civilians travel overseas annually—a constant source of imported cases. Transfusion-associated malaria has increased. Despite the rising rate of heroin abuse in this country, malaria associated with shared needles is very rare on the East Coast, possibly owing to the frequency with which illicit drugs are diluted with quinine, but has been responsible for at least one malaria outbreak in California.

The Parasite

Malaria is transmitted by the bite of female *Anopheles* mosquitoes. The parasite disappears from the blood of man within 30 minutes, and then spends a minimum of six days developing in the liver parenchymal cells (primary exoerythrocytic cycle). The released merozoites then enter red blood cells and undergo development from ring to schizonts, which release new merozoites in 48 to 72 hours. Even with multiple infections, one strain becomes dominant, and the release of merozoites (schizogony) becomes synchronous, each release in the non-immune being associated with a paroxysm of fever. Merozoites may also re-enter liver cells and remain dormant, only to reappear at a later date, causing relapses (secondary exoerythrocytic cycle); since *Plasmodium falciparum* has no secondary exoerythrocytic cycle, clinical illness is rarely seen longer than one year after exposure.

Some parasites are destined to become gametocytes, which are infectious for a suitable vector for about 12 hours. The mosquito must ingest both a male and female gamete to develop sporozoites infectious for man. Not all *Anopheles* mosquitoes are equally effective vectors for different strains of malaria, and the time required for the infectious parasite to develop in a suitable vector (average 12 days) depends on climatic conditions. These requirements plus luck explain the rarity of introduced malaria in the United States today.

The Clinical Picture

There are four human malaria parasites of medical importance. *Plasmodium falciparum*, the cause of malignant subtertian malaria, is the only type which causes death in the absence of other disease. *Plasmodium vivax*, benign tertian malaria, is the most common; clinical manifestations are usually limited to fever and anemia. *Plasmodium malariae*, quartan malaria, is similar to *P. vivax*, but noteworthy for its potential to cause relapses long after exposure (possibly after 45 years) and the association of nephrosis and immune-complex renal disease with chronic infection.⁶ *Plasmodium ovale* clinically simulates *P. vivax* infection; it is rare (except in West Africa) and will not be considered further.

The most characteristic clinical manifestation of all forms of malaria is the cyclic febrile paroxysm which recurs every 36 to 72 hours. Headache and malaise are shortly followed by a cold stage with pronounced cutaneous vasoconstriction and polyuria. This stage lasts for 15 minutes to one hour. Chills are most pronounced in quartan malaria, least so in *falciparum* malaria, with *vivax* malaria holding an intermediary position. Toward the end of this stage the temperature begins to rise, the patient experiences hot and cold sensations, and finally a sustained hot stage with vasodilatation. Headache, nausea and vomiting are common. This stage lasts from two to six hours and is followed by a profuse diaphoresis accompanied by a return of body temperature to normal over the next two to four hours. The patient then feels better although fatigued. Although the fever usually occurs in the afternoon or early evening, malaria is one of the few causes of morning fever; this finding plus the duration of the paroxysm should suggest the diagnosis of malaria. Partially immune persons experience milder illness, and some non-immunes may show sustained fever, and *P. falciparum* infection may progress rapidly to the death of the patient.

Physical findings other than those of the paroxysm are usually not striking. Splenomegaly is most common with chronic infections and may be absent in acute illness. Severe neurologic and psychiatric aberrations including coma (cerebral malaria), hyperpyrexia with sustained temperature elevations in excess of (42°C) (108°F) pulmonary edema, acute renal failure, hematemesis, dysentery or choleraic stools, or severe jaundice may occasionally dominate the clinical manifesta-

tations of *P. falciparum* infections; these findings are rarely if ever seen with vivax or malariae infections.

Laboratory Abnormalities

Anemia is the most consistent laboratory abnormality, and it is to some degree related to the degree of parasitemia; hence *falciparum* parasites which invade all stages of erythrocytes are likely to cause more severe anemia than vivax infections, which invade reticulocytes preferentially. However, both parasitized and non-parasitized erythrocytes are destroyed at an accelerated rate; it is not unusual for the red cell destruction to be three times the number of parasitized red blood cells.⁷ In vivax malaria, normal bone marrow response to anemia may be suppressed and no reticulocytosis seen; in *falciparum* malaria reticulocytosis is usually present. Both leukopenia and thrombocytopenia are common. About half of patients have albuminuria.

Pathophysiology

Remarkably little is known about the pathophysiology of malaria. With each sporulation in blood, parasitized red cells are destroyed. The mechanism of the paroxysm in association with sporulation is totally unknown, although the release of malarial pigments, red cell breakdown products and unidentified toxins are widely conjectured. The mechanism of the anemia is also enigmatic: observations that transfused red blood cells as well as unparasitized red blood cells have a shortened survival, that unparasitized red blood cells have increased osmotic fragility, and the occasional but rare demonstration of a positive Coombs test have led to the supposition that an antibody reaction facilitates increased splenic sequestration and destruction of red blood cells.⁸ Recent studies in monkey malaria show an alteration in sodium transport in parasitized and unparasitized red blood cells, which could accelerate red cell destruction; increased red cell sodium occurs by the second or third day of parasitemia, slightly earlier than detectable fluorescent antibody, suggesting a circulating toxin.⁷

Red cells parasitized with *P. falciparum* tend to stick to the walls of capillaries of internal organs, where they presumably interfere with blood flow and oxygen transport. With early treatment these

changes are reversible; if treatment is delayed the patient may die despite decreasing parasitemia. The outlines of small blood vessels lined with parasitized erythrocytes have been seen on microscopic examination of sections of brain from patients who died of cerebral malaria. Acute renal failure may be due to this mechanism or a sequel of black water fever (hemoglobinemia and hemoglobinuria). Sometimes, acute renal failure follows intermittent quinine treatment for recurrent malaria, and it sometimes complicates primaquine therapy in patients with glucose-6-phosphate dehydrogenase deficiency. Acute renal failure and other manifestations of severe *falciparum* malaria in some cases appear to be due to an associated consumption coagulopathy.⁹

Diagnosis

A high index of suspicion and a carefully detailed travel history are necessary for diagnosis. Only a short stop-over in an endemic area, such as debarkation for an hour between planes, which might well be overlooked in a recitation of itinerary, may be sufficient to acquire fatal malaria. In light of the prolonged interval between the acquisition of *P. malariae* and symptoms, a remote as well as immediate travel history must be obtained. Splenectomy or other surgical procedure, anesthesia, childbirth, and possibly steroids, can activate a latent infection.

The diagnosis cannot be relegated in good conscience to the laboratory. Fisher¹⁰ reported three of five patients with fatal cases of *falciparum* malaria had positive blood smears on admission which were overlooked by the laboratory.¹⁰ Despite the heavy parasitemia that can occur with *falciparum* malaria, the small size of the ring forms and the usual absence of the larger trophozoites and schizonts from the peripheral blood may thwart detection of this infection without a specific search for the parasite. In vivax infections less than 2 percent of red blood cells are infected, and in malariae the proportion is usually less than 1 percent. Although the morphologic features of the parasite are more easily identified by the novice on thin films stained with Giemsa, thick films are necessary for diagnosis in many cases. One drop of blood spread in a circular fashion with the lancet to about the size of a dime makes a good thick smear. The thick smear, unlike the thin smear, is not fixed with methyl alcohol before staining; the aqueous solution of Giemsa then

TABLE 3.—*Distinguishing Features of Plasmodia*

	<i>P. falciparum</i>	<i>P. vivax</i>	<i>P. malariae</i>
Incubation period ¹	7-12 days	9-15 days (280 days)	30-40 days (over 20 years)
Duration untreated infection	1 year ²	3 years	over 20 years
Cyclic paroxysm	every other day	every other day	every third day
Age RBC parasitized	all	reticulocytes	old RBC
Appearance ring forms	VERY SMALL, "DOUBLE-DOT" RINGS: marginal (accolé) forms	small and large rings; one chromatin dot	like <i>P. vivax</i>
Double infection (2+ rings)	very common	not rare	rare
Appearance of older trophozoites	RARELY SEEN IN PERIPHERAL BLOOD	HIGHLY PIGMENTED AMEBOID	BAND FORMS (only seen in thin films)
Appearance of mature schizont	fills 2/3 RBC average; 16 merozoites	fills entire RBC; average 16 merozoites	fills almost entire RBC; average 8 merozoites symmetrical (daisy, ROSETTE)
RBC Pigment	only 1-3 solid blocks (Maurer's dots)	marked (20+) (Schuffner's dots)	quartan stippling
Size of parasitized RBC	normal	LARGE (up to 2 X nl.)	normal

Features in capital letters represent the most helpful differential points in morphology. In addition the gametes of falciparum malaria are crescents (banana-shaped) and differ from all other human malaras.

¹The incubation period noted is an average; some patients experience the first clinical attack at considerably longer periods after presumed

exposure. Inadequate or prematurely withdrawn chemoprophylaxis also alters the incubation period.

²Some cases of *P. falciparum* are on record 3½ years after presumed exposure; usually clinical attacks in unsuppressed patients occur within 6 months of exposure.

lyses the red blood cells, so that parasites must be recognized without the assistance of erythrocyte morphology.

The specific type of malaria has important prognostic and therapeutic implications. Table 3 outlines the distinguishing features of the three common types of human malaria. Malaria parasites are best observed in capillary (fingerstick) blood in the period preceding the paroxysm, but can usually be found at any time and there is no rationale for waiting for the next anticipated fever spike. Indeed, with falciparum malaria, plasmodia are most numerous in the peripheral blood during the fever-free interval. A heavy parasitemia with *P. falciparum* can develop within 24 hours and carries a poor prognosis despite therapy. Repeated careful search will disclose the parasites in the peripheral blood of virtually all patients clinically ill with malaria; rarely, in severe *P. falciparum* infections, the parasites may be confined to the vascular system of internal organs and empirical therapy is required. Asymptomatic cases have been diagnosed on occasion by bone marrow study.¹¹ Provocative tests (to release parasites from internal organs such as the spleen, for example) utilizing epinephrine are both unreliable and dangerous and should be abandoned. Fluorescent antibody tests, rarely required for the

diagnosis of acute malaria, may be useful for determining the cause of previous paroxysms of fever as well as screening of potentially infected blood donors; positive reactions to these tests continue for more than five years after departure from the endemic area and after apparent eradication of infection.¹²

Treatment

Many drugs are available for the treatment of malaria. A slight modification of the treatment regimen suggested by the National Institutes of Health is outlined in Table 4. There are two types of cure for malaria: clinical cure—that is, termination of acute attack—and radical cure, or termination of infection. For clinical cure a drug is required which acts rapidly on blood forms, a schizontozide. The most effective drug for this purpose, for all strains of chloroquine-sensitive malaria, is still chloroquine. Chloroquine also produces a radical cure of non-resistant falciparum malaria, which has no secondary exoerythrocytic cycle. In other malaras radical cure requires chloroquine plus the addition of a drug effective against the liver phase of the parasite. The drug of choice is primaquine. A patient with latent vivax malaria—that is, low-grade asymptomatic parasitemia—will get a radical cure with prima-

TABLE 4.—*Treatment of Malaria*

<i>Regimen</i>	<i>Drug</i>	<i>Dose and Route</i>	<i>Duration</i>
1. All types of malaria	Chloroquine phosphate	1.0 gm (600 mg base) followed by 0.5 gm po	1 day
	Chloroquine phosphate	0.5 gm po	day 2 + day 3
	Primaquine	15 mg base* po	day 1 through 14
2. Patients with falciparum malaria who have not responded to or who have relapsed following regimen 1 (above) or who have never received treatment but who are gravely ill, or who have acquired malaria in the Central Highlands of Vietnam	Quinine sulfate	0.65 gm (two tabs, 5 gr each) q 8 h po	day 1 through 14
	Primaquine	15 mg base* po	day 10 through 24
3. Patients with falciparum malaria who are comatose, markedly hyperthermic, have acute renal failure, or vomiting	Quinine dihydrochloride	600 mg in 600 ml NS, very slowly IV q 8 h	change to po drug regimen 2 as soon as possible (by stomach tube if necessary)
4. Patients with falciparum malaria who have recrudescence following 2 or 3 above; or who have persistent parasitemia despite clinical response to 2 or 3	Pyrimethamine	50 mg daily po	day 1 through 3
	Sulfadiazine	0.5 gm q 6 h po	day 1 through 5

*Primaquine is not essential for radical cure of falciparum malaria which has no secondary exo-erythrocytic cycle; the frequency of mixed infection with other malarias which do have a secondary exo-erythrocytic cycle, and may relapse at a later date, warrants use of this drug.

Note: Quinine therapy is associated with orthostatic hypotension; it should only be given to patients at bed rest whose blood pressure is monitored frequently. Intravenous quinine causes a serious risk of hypotension and arrhythmia and should be avoided or discontinued whenever possible.

quine alone. The gametocytes of all forms of malaria are eradicated by primaquine for three days.

The treatment of falciparum malaria constitutes a medical emergency; irreversible disease can develop within 24 hours. Fortunately, less than 40 percent of malaria imported from Vietnam has been due to *P. falciparum*. Resistance to chloroquine is documented only for falciparum malaria; in 10 to 20 percent of cases Vietnam falciparum malaria is completely resistant to chloroquine, (i.e. will not have a clinical cure) and in 60 to 70 percent of cases it is partially resistant (will have a clinical but not a radical cure). The great majority of relapses occur within one month of therapy. When dealing with falciparum malaria which has relapsed after chloroquine therapy or has not responded to the drug, or when the clinical illness is very severe, quinine is the drug of choice. While quinine produces a clinical cure in almost all cases, it brings about radical cure in only 25 percent. Radical cure in patients who have had relapse after the above therapy can usually be achieved by a combination of pyrimethamine (Daraprim®) and sulfadiazine.¹³ Sulfamethoxazole (Fanasil®, an isomer of madribon) is a long-acting sulfonamide which has proved useful in Vietnam when combined in a single dose with pyrimethamine.¹⁴ It is not available for clinical use in the United

States. The management of complications of malignant malaria, pulmonary edema, cerebral malaria and acute renal failure has been reviewed elsewhere.^{15,16}

Prophylaxis is also divided into two types, causal and suppressive. Causal prophylaxis prevents demonstrable infection; both Daraprim®, now in disuse because of resistance, and primaquine, rarely used because of toxicity of prolonged administration, are causal prophylactics. Suppressive prophylaxis, inhibition of erythrocyte phase and suppression of symptoms, with weekly chloroquine (300 mg base) is preferred for travelers to all areas without known chloroquine-resistant malaria. Prophylaxis should be started two weeks before going to an endemic area and continued for at least a month after return. In areas where chloroquine resistance exists, either sulfamethoxazole (1 gm a week) or the parent sulfone, dapson (25 mg four times a day), has proved effective; but it should be noted that daily use of dapson (DDS) in Vietnam has sometimes been followed by severe, even fatal bone marrow depression, and its routine use as a prophylactic can no longer be recommended. Failure to take medications regularly or for a sufficient period after return to the United States explains some but not all of the imported malaria seen in Vietnam veterans.

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A New Circumcision Device

A Preliminary Report

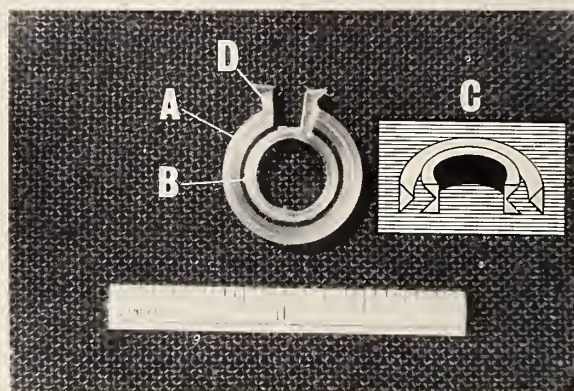
LAWRENCE D. FREEDMAN, M.D., *La Mirada*

A NEW, disposable circumcision clamp* made of butyrate plastic has been used in the circumcision of 40 infants, the operation taking usually less than one minute.

The clamp (see illustration) consists of two rings, one encircling the other, which are attached at one point. The outer ring (A) is flexible, the inner ring (B) rigid (inset in illustration). The inner surface of the outer ring is V-shaped in cross-section and the inner ring has a matching V-shaped groove on its outer surface (C). Between the two rings is just enough space to receive the foreskin. Attached to the outside ring are two small knobs (D) which, when drawn together and clamped, hold the outer ring snugly against the inner, hemostatically compressing the foreskin between them.

* Available from Quik-Circ, 1541 Wilton Way, La Habra, Ca. 90631. Submitted October 5, 1970.

Reprint requests to: 15744 East Imperial Highway, La Mirada, Ca. 90638 (Dr. L. D. Freedman).



Circumcision is performed by making the usual dorsal slit and then slipping the ring around the foreskin and down to the base of the glans. The knobs are then tied together and the redundant foreskin is excised. As with currently used plastic clamps, this device remains in place and usually falls off within one week, leaving a healed circumcision wound.

In the 40 operations there were no complications such as hemorrhage or infection. The great advantage of this device over other currently used plastic clamps is that with it circumcision can usually be performed in less than one minute.

Dupuytren's Contracture of the Fingers

A Simplified Approach to the Surgical Treatment

RICHARD I. GONZALEZ, M.D., *San Mateo*

■ *Hematoma formation, delay in healing, pain, stiffened finger joints are complications that sometimes follow classical surgical approaches to Dupuytren's contracture. A new surgical approach to the disease that can correct the contractures without the attendant morbidity is urgently needed. By treating Dupuytren's as any other scar contracture (division of the contracting soft tissue at its point of maximal tension and interposing normal free full-thickness skin) postoperative morbidity can be greatly decreased. Full return of function was achieved within 21 days following operation in 85 percent of the cases in which finger contractures were present before operation. Contracture release of 100 joints was done by this means, with loss of only one graft and without recurrence of the disease. This technique offers simple surgical control of progressive and recurrent Dupuytren's contracture of the fingers with minimal postoperative morbidity.*

POSTOPERATIVE MORBIDITY—delayed healing, joint stiffness and pain — following the surgical treatment of Dupuytren's contracture, is well known. As Howard¹ has stated, "The only major problem in the surgical treatment of Dupuytren's contracture is the prevention of postoperative stiffness of the small finger joints." And as Shaw and Barclay² noted, "The overriding consideration leading to a successful result is to restore a healed hand to normal use within three weeks of operation." The degree of postoperative morbidity, in my experience, has been almost proportionate to the extent of the surgical procedure: The more extensive the procedure, the greater the morbidity. The simplest surgical procedure, subcutaneous fasciectomy, car-

ries very little morbidity; but in my experience, in progressive disease it provides only temporary relief of the contracture. However, radical palmar fasciectomy with or without finger dissection, though carrying a high degree of postoperative morbidity, does not guarantee prevention of recurrence. In 1951 Hamlin³ recognized this seeming enigma and advocated limited palmar fasciectomy in the hope of reducing postoperative morbidity. He recommended excision of the diseased fascia alone and was able to return his patients to "usual occupation" 12 to 30 days after operation, in contrast to the average of 118 days following the classical radical fasciectomy.

In Hamlin's report, however, there was no indication as to the extent of finger contractures against localized palmar involvement. In 1961 Hueston⁴ reported on a larger series of patients

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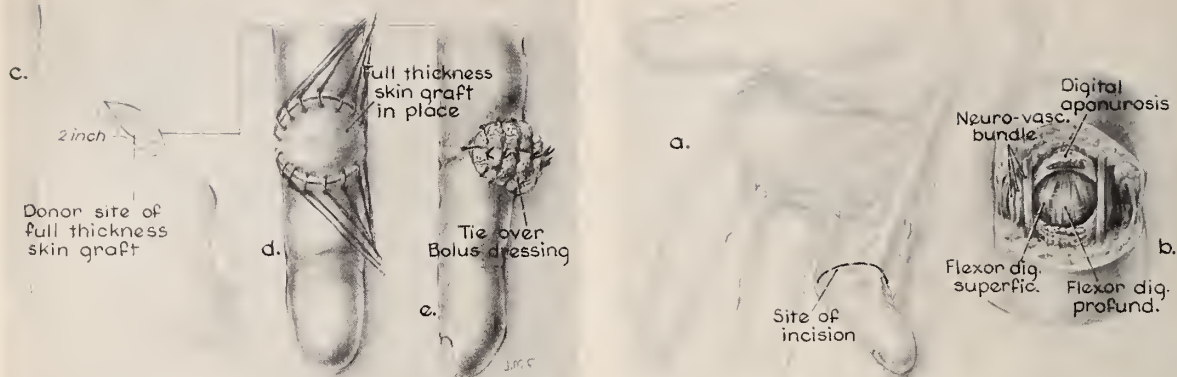


Figure 1.—Technical steps in the release of Dupuytren's contracture, utilizing inset of full thickness skin grafts.

a) *Step 1.* Transverse skin incision across point of maximal tension.

b) *Step 2.* Before subcutaneous fascial band is cut the neurovascular bundles are identified, mobilized and protected. These bundles are often out of their normal anatomical position and may be hidden within the fascial band.

c) *Step 3.* A full thickness skin graft is taken from a hairless area overlying the inguinal ligament. The skin in this area is quite thin and the resultant donor defect is easily closed by a simple continuous suture, particularly if a bottom layer of partial thickness of dermis is left in depths of donor area.

d and e) *Step 4.* The free full skin graft is carefully sutured in place with interrupted 3-0 black silk sutures which are left long and tied over a bolus of wet cotton. Care should be taken to tie the sutures in the vertical direction only, for tightly tied transverse sutures may compromise the blood supply of the dorsal skin bridge. The finger is immobilized in the extended position by a padded volar plaster splint. Uninvolved fingers are left free, and early motion encouraged. The bolus is removed at seven days and the skin sutures at ten days. Active motion is encouraged after the removal of the bolus dressing.

for whom local fasciectomy plus multiple Z-plasty had been used to lengthen the secondarily shortened volar skin over the contracted fingers. Twelve and a half percent of these patients recovered full flexion within three weeks, and 84.5 percent within six weeks after operation. In neither series was recurrence a major problem. In the hope of further reducing postoperative morbidity and approaching the ideal of full return of function within three weeks, I substituted inset full-thickness skin grafts for Z-plasty to overcome volar finger skin shortness. By transecting the contracting fascial band and skin at its point of maximal tension and inserting full-thickness skin grafts into the defect, dissection and undermining is kept to a minimum and healing and return of function is rapid. The use of full-thickness skin grafts as an adjunct to the treatment of Dupuytren's contracture is not new. Gordon,⁵ Skoog⁶ and Hueston¹ have all recommended the use of Wolff grafts for replacement of avascular palmar skin. However, no one to my knowledge has used them as insets or additions to lengthen shortened skin. I have released

100 contracted finger joints in this manner over the past 11 years. In 85 percent of cases full flexion and extension were restored within 21 days after operation and to date there have been no recurrences of the contractures.

Technique

Under either general or local anesthesia, the point of maximal tension of the contracting band is marked and a transverse skin incision is made to each mid-lateral line (Figure 1, a) The neurovascular bundles (Figure 1, b) are identified and mobilized by spreading longitudinally with sharp-pointed scissors. After the bundles are well visualized, all fascial bands are totally divided transversely. This usually permits complete extension of the finger. Shortened volar joint capsules may restrict full extension but are best mobilized postoperatively by the use of a dorsal clock-spring splint and not by capsulotomy. The proximal palmar remnant of the fascial band can be excised through short vertical or transverse incisions. This step can be elim-



Figure 2.—Preoperative condition in a 57-year-old male (A and B). There is a moderate contracture at the proximal joints of the left long (-42°), ring (-40°) and little (-30°) fingers. The little finger also lacks 17° at the middle joint. Contracture of this type could adequately be treated by conventional palmar fasciectomy, however, by utilizing inset full thickness skin grafts plus limited fasciectomy under local anesthesia (C), the release of the contracture was accomplished with minimal operative and postoperative morbidity. Pictures D and E demonstrate the range of motion immediately after the removal of the skin sutures (ten days after operation). Pictures F, G and H show range of motion 20 days after operation. The full thickness skin grafts were taken from the instep of the foot. There has been no recurrence of progression of the disease since operation (21 months).



A



E



B



F



C



G



D

Figure 3.—Shown are hands of a 60-year-old man who had similar contractures of both little fingers. The left little finger contracture was released on September 15, 1966, by means of an inset full thickness skin graft taken from the groin. The contracture of the right little finger was similarly released January 16, 1968, by means of a graft taken from the instep of the foot. A three-year postoperative photograph of the groin graft and one-year follow-up of the foot graft demonstrate full and equal flexion and extension of both fingers (C,D,E,F). A close-up (G) of the grafts demonstrates the difference in texture and appearance of the two grafts.



Figure 4.—Hand of a 62-year-old man with pronounced contracture of middle (-58°) and distal joints (-60°) of left little finger (A and B). Patient also had a moderate middle joint contracture of left index finger (-55°). Contractures were released under local anesthesia with two inset full-thickness grafts taken from the groin. Result seven months after operation is shown in C, D and E. The extreme contracture of the little finger at the middle and distal joints probably could not have been released by any other approach, except by a cross-finger flap with attendant morbidity.

inated without jeopardizing the end result, as remnants of the released fascial bands soften and largely disappear.

The site of operation is then changed to the donor site (Figure 1, e)—either the groin or instep of the foot. Foot skin most resembles finger skin in texture, color and thickness. However, the size of the graft that can be taken from the instep is limited unless one is willing to split-graft the donor site. Another disadvantage of using the foot as a donor site is the necessity to restrict weight-bearing until healing is complete. The groin is a better donor site for large grafts,

and the ease of closure there is a further advantage. One disadvantage is hyperpigmentation of the skin in that area, particularly in dark-skinned patients. If one leaves a thin layer of dermis in the base of the donor site, closure is greatly facilitated and undermining is not necessary. Quite large donor areas can be closed with a simple running suture. The skin for grafting should be taken from the lateral aspect of the groin, as there are few hair follicles there. The free graft is carefully sutured into the denuded area of the finger (Figure 1, d)

The sutures are placed 2 to 3 mm apart, are



Figure 5.—Hand of 67-year-old man who had contracture of the first cleft and all the fingers of his left hand (A). The contractures were released by three full-thickness inset grafts and a limited palmar fasciectomy under local anesthesia with full recovery of function (B and C). Usually there is little if any functional disability in Dupuytren's contracture. However, when there is involvement of the first cleft, opening of the hand for grasp is limited.

left long and are tied over a bolus of wet cotton (Figure 1, e) Postoperative bleeding, hematoma formation or "graft take" have not been problems. However, if a graft does not take, an immediate cross-finger flap is necessary to protect the exposed flexor tendons. A volar plaster splint is incorporated in the dressing, to keep the finger at rest. The bolus is removed at seven days and skin sutures at ten days.

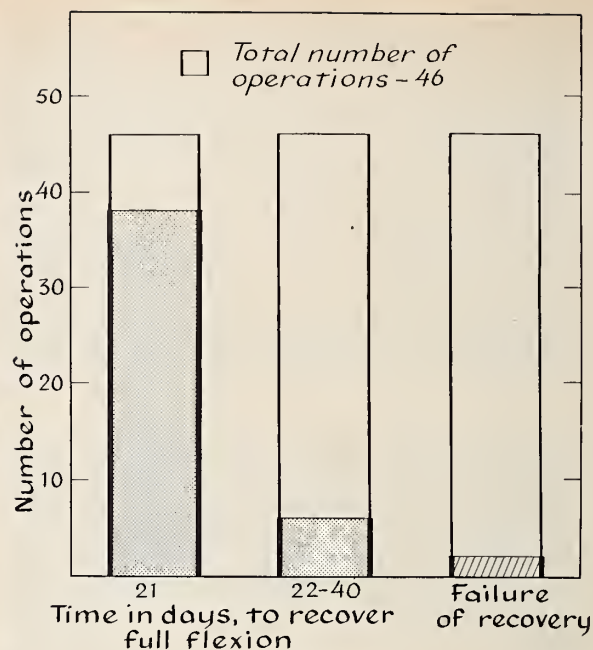


Chart 1

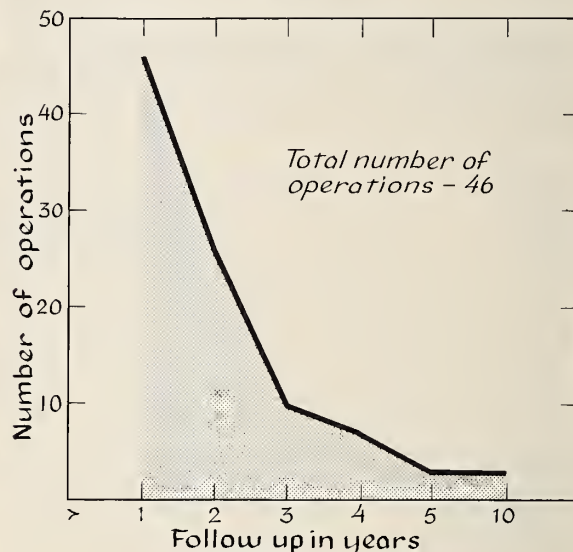


Chart 2

Supervised active exercises are carried out until full flexion and extension are achieved. To achieve maximal flexor power in the small finger joints, the patient should stabilize each finger joint by firmly holding the finger just proximal to each joint and vigorously contracting the flexor musculature. Only by such vigorous exercise can early return of full flexion be achieved. It is the physician's responsibility to make certain that these exercises are carried out continuously and properly.

TABLE 1.—Clinical Data on 39 Patients with 46 Operations for Release of 100 Finger Joints

Patients	39
Male	30
Female	9
Age range (years).....	18-91
Average age	58.6
Past History	
Arthritis	19
Bursitis	12
Heart "trouble"	5
Family History of Dupuytren's Contracture.....	12
Maternal	6
Paternal	6
Previous Rx Treatment	
Surgical	17
Xradiation	1
Cortisone	1
Ultra sound	1
Distribution of Disease	
Palm	31
Thumb	6
Index finger	4
Long finger	12
Ring finger	17
Little finger	34
Contracted Joints	
Proximal joint	46
Average lack of extension.....	-46°
Middle joint	44
Average lack of extension.....	-49°
Distal joint	10
Average lack of extension.....	-33°
Total Number of Operations.....	46
Type of Operation	
Limited palmar fasciectomy plus full thickness skin grafts (finger).....	31
Full thickness skin grafts only (finger).....	15
Donor Sites	
Groin	48
Foot	12
AnteCubital Fossa	3
Total free full thickness skin grafts.....	63
Anesthesia	
General	27
Local	15
Operative Results	
Postoperative morbidity (Chart 1)	
Recovery full flexion 21 days after operation	38 (83%) Figure 3
Recovery full flexion 40 days after operation	44 (96%)
Recurrence	0
Progression	0
Follow-up (years)	
Average (Chart 2).....	3.5
Range.....	1.5 to 11.5
Complications	
Nerve damage	0
Hematoma	0
Infection with loss of graft.....	1

This series (details in Table 1) demonstrates the usual sex and age distribution as well as the association of Dupuytren's contracture with other forms of coexisting collagen disease. The high incidence of previous surgical treatment indicates the applicability of this technique to recurrent or progressive Dupuytren's contracture. The low incidence of palmar involvement is a reflection of the fact that no cases of palmar involvement without finger joint contractures were included in this series.

Discussion

Most grafts healed well within ten days following operation. In a few there was delay in healing of the superficial layers of the graft. This did not interfere with the beginning of vigorous active exercises. In thirteen cases full flexion was achieved immediately after the bolus and sutures had been removed from the grafts (ten days). One full-thickness skin graft was "lost" due to hemorrhage and secondary infection. This was in an alcoholic woman who broke the splint on her hand in a fall three days after operation, and as she did not return for postoperative visits the accident was not discovered. In this case both tendons and neurovascular bundles sloughed. It is probable that if a cross-finger flap had been placed on the exposed tendons soon enough, the function of the finger could have been preserved. One other patient, although improved, did not recover full flexion and extension of his finger. He was a 91-year-old man whose little finger had been firmly flexed into his palm for 25 years. The middle joint did not respond to postoperative splinting.

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Gonorrhea Today

Problems of Diagnosis, Management, Treatment

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GONORRHEA HAS RISEN to epidemic proportion in the United States. The number of reported cases increased sharply from 246,697 in 1960¹ to 494,227 in 1969.² Most cases, however, are not reported. The total number is now estimated to be over 1.5 million yearly.³

Confusion in diagnosis and therapy have increased along with the incidence of gonorrhea. When the antibiotic era began, physicians assumed that the disease would soon be eradicated. Gonorrhea has escaped control, let alone eradication, for several reasons. Most women who have gonorrhea are asymptomatic. The Gram-stained smear will be negative in many patients, particularly women, who have gonorrhea. Relative resistance of gonorrhea to penicillin has developed and is increasing. Prophylaxis has lapsed with the advent of female oral contraceptives.

Diagnostic Problems

The Gram-stained smear is a reliable method of laboratory diagnosis in the male with a thick yellow urethral discharge.⁴ Laboratory diagnosis is more difficult when a gray watery discharge is present. Females with gonorrhea seldom have a purulent discharge. Approximately 80 percent of them are asymptomatic and only have a mild endocervicitis. Cervical and urethral smears are negative or inconclusive in at least half the cases. In a comparison of slide and culture techniques,

diagnostic accuracy doubled when cultures were obtained in asymptomatic female contacts. Pariser and Farmer⁵ showed that 44 percent of asymptomatic female patients with known contacts did not have a positive culture while 71 percent did not have a positive smear. There is no way of predicting which of these patients will turn up positive and which negative.

Culture methods first employed were unsatisfactory because specimens were contaminated by bacteria which outgrew the more slowly developing gonococcus. Early attempts to reduce contaminating organisms were not helpful since many gonococcal strains were killed by inhibiting agents. The Thayer-Martin culture medium was introduced in 1964.⁶ This culture medium currently uses vancomycin to inhibit Gram-positive contaminants, sodium colistimethate for gram-negative flora, and nystatin to inhibit yeast.⁷ The Thayer-Martin culture technique is the best means of laboratory diagnosis of gonorrhea at the present time, but false negative reports still occur in significant numbers.

Since the gonococcus is an intracellular organism, no further improvements in culture techniques by *in vitro* methods are anticipated. Laboratory diagnosis cannot be fully relied upon in this disease. Treatment of suspected females is mandatory to keep them from becoming a chronic reservoir of the disease, a reservoir which Willcox⁸ aptly termed "the promiscuous female pool."

The male patient presents other diagnostic problems. The physician may not be able to obtain urethral exudate for examination. In the absence of discharge, smear and culture of urinary sedi-

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ment has been rewarding in some cases.⁹ The male patient may be seen with a history of exposure but before symptoms begin. Pariser et al¹⁰ found laboratory evidence of gonococcus following prostatic massage in 26 of 98 asymptomatic male contacts seen six days following exposure. For both male and female patients, it is clear that treatment should be based on history. The laboratory should be consulted for confirmatory diagnosis or evaluation of treatment which has already been initiated on the patient's first visit.

Therapeutic Problems

The treatment of gonorrhea with penicillin has become increasingly confusing. Penicillin, though still effective, can no longer be considered a wonder drug for gonorrhea. Problems were forecast in 1958 by Epstein when United States troops treated in Korea failed to give the anticipated response to penicillin.¹¹ Although he gave the recommended injections of 600,000 units of procaine penicillin G for five days, the failure rate was 20 percent. A similar rate of penicillin failure was noted in England about the same time.¹²

It became evident that decreases in susceptibility of some strains of *N. gonorrhea* was occurring. None of the strains encountered before 1954 had shown resistance to 0.05 units of penicillin per milliliter of serum *in vitro*.¹³ Subsequent studies in Germany showed a progressive change in resistance from 0.0074 units of penicillin per ml *in vitro* in 1956 to 0.0218 units per ml in 1958, to 0.164 in 1961, and then to 0.25 units per ml in 1964.¹⁴ Similar *in vitro* resistance increases were found in other parts of the world including Australia¹⁵ and Canada.¹⁶

In 1966 the resistance of the gonococcus to penicillin *in vitro* was assessed in various areas of the United States. On the East Coast 7.3 percent of strains were resistant to 0.30 units of penicillin per ml, with the percentage increasing westward to 33 percent in California.¹⁷ Recently it has been reported that 14 percent of strains are resistant to 0.5 units of penicillin per ml of serum.¹⁸ These figures do not mean that gonorrhea is no longer sensitive to penicillin but that there has been a progressive relative resistance requiring higher and higher doses of penicillin to effect good cure rates. They also demonstrate the varying susceptibility of the organism in different geographical areas.

A single dose of 2.4 million units of procaine penicillin G was recommended by the United States Public Health Service in 1965. Holmes et al¹⁹ studied gonorrhea in U.S. military personnel in the Far East. They found that procaine penicillin G 2.4 million units in a single dose, resulted in a failure rate of 29 percent for shipbound sailors. When 2.4 million units of procaine penicillin G was given intramuscularly on two successive days to Air Force personnel in Viet Nam, the failure rate was 25 percent.²⁰ If 2.4 million units of benzethine penicillin G was added on the third day, the failure rate was reduced to 9 percent.

In 1965, Lucas et al²¹ evaluated different penicillin treatment schedules for women. Procaine penicillin G in a single injection of 2,400,000 units gave a failure rate of 8.7 percent. The failure rate for 4.8 million units was 4.0 percent. A failure rate of 3.8 percent was noted by Shapiro and Lentz²² using 2,400,000 units of aqueous procaine penicillin G with 2,400,000 units of procaine penicillin G in oil. At present, the United States Public Health Service recommends 2.4 million units of aqueous procaine penicillin for males and 4.8 million units for females.

These problems led to a search for suitable substitutes for penicillin in the treatment of gonorrhea—safe agents with good cure rates and minimal side effects. Most attention has been focused on the tetracyclines. Epstein¹¹ found that most of his penicillin failures in 1958 responded to oxytetracycline. Shapiro and Lentz²³ gave women at the Public Health Venereal Disease Clinic in Philadelphia oxytetracycline 250 mg intramuscularly and 1.0 gram orally on a single visit. Of 120 patients with a culture diagnosis of gonorrhea, 110 had three consecutive negative cultures following therapy. Ashmalla et al²⁴ found that with oxytetracycline 500 mg intramuscularly and 250 mg orally every six hours for seven days for men the failure rate was 1.8 percent. Holmes et al¹⁹ had no failures in 30 men given tetracycline 1.5 gram orally, then 500 mg every six hours for four days. Maurer and Schneider,²⁰ using the same schedule for 141 men, had 7 percent failures. In these last two studies, much less post-gonorrheal urethritis was noted than in patients who were treated with penicillin.

Attention recently has turned to doxycycline, a new semi-synthetic tetracycline which chemically is α -6-deoxy-oxytetracycline. This drug is distinguished from other members of the tetracycline

family by a more efficient gastrointestinal absorption which is not significantly affected by food or milk, and also achieves high blood levels earlier and has a longer serum half-life. Single doses of 300 mg of doxycycline have been used in Montreal with a failure rate just over 5 percent.²⁵ However, the length of time before re-examination was not specified in the report. With single doses of 250 mg given to 169 males by Domesik et al²⁶ the failure rate was just under 5 percent. In this study patients returned for re-examination in 96 hours. One of us (W.H.S.) used a single dose of 300 mg of doxycycline briefly but met with a failure rate of 62 percent with re-examination in seven days.¹⁷ Unless therapy is continued to include three life cycles of the gonococcus, suppression without cure apparently can take place.

The Physician's Legal Responsibilities

The physician's obligation under the law must be considered in cases of gonorrhea. Statutes describing the physician's responsibility vary from state to state. In California, Title 17, Section 2500 of the Administrative Code states that it is the duty of the physician in a case of suspected venereal disease to notify the local health authority immediately. In addition, Section 2536h states that the attending physician must endeavor to find the source of the infection, including any intimate contacts made while the patient's disease was communicable. He must make an effort to bring the contacts in for examination and, if necessary, treatment. If such contacts are not under care of a physician within ten days, they must be reported to the health officer. The statutes indicate that all information given to the local health authority will be kept confidential.

Section 3198 of the California Health and Safety Code states that any person who refuses to give information or reports having to do with venereal disease is guilty of a misdemeanor. (A legal consultant on this point thought it reasonable to conclude that a physician who does not report a suspected case of gonorrhea to the local health office could be convicted of a misdemeanor for failing to do so.)

In 1969, there were 36,641 cases of gonorrhea reported in the County of Los Angeles.²⁷ Public health investigators interviewed all male patients for their contacts. The contacts were in turn referred to a public health office or private physi-

cian. Patients or contacts who refused to cooperate were served with an order to appear at a public health office. Each year in Los Angeles County it is necessary to serve such an order on about 35 persons. The eight or so who still refuse to be examined are taken to court for not complying with the law. They are usually ordered to go to a public health office and are given a one-year summary probation.

The State of California supplies physicians and institutions with confidential morbidity report forms. They should be used for reporting all communicable diseases including gonorrhea to the local health officer.

Management of Patients with Gonorrhea

The district health centers of the County of Los Angeles have established a protocol for the management of gonorrhea which is sensible and expedient.

Past and present venereal history is obtained from each patient. Men are considered symptomatic if they complain of a urethral discharge. Women are considered symptomatic if they have lower abdominal pain, dysuria or a vaginal discharge. A specimen of blood for Venereal Disease Research Laboratory (VDRL) test is drawn. The genitalia are examined for lesions. In males a smear of the urethral discharge, if present, is made with a cotton applicator onto a glass slide. A charcoal-impregnated applicator is used to obtain urethral discharge for culture. If no discharge is present, urine is obtained for smear and culture of the spun sediment. In females, smears of the urethral meatus and cervical os are obtained for Gram-staining. Cultures are collected by swabbing the same areas. All culture swabs are placed in Stuart's transport medium.^{28*}

Specimens are sent to the central Los Angeles County Public Health Laboratory. Smears are read as positive, negative or inconclusive for Gram-negative intra-cellular diplococci. Cultures are obtained by plating the swabs onto Thayer-Martin medium and incubating the plates anaerobically at $35^{\circ} \pm 0.5^{\circ}\text{C}$. At 48 hours oxidase reagent is placed on the plates. Colonies which turn dark (oxidase positive) are smeared for Gram-staining. A positive Gram-stain is read as a positive culture.

Therapy is instituted on the first clinic visit for

*Holding Transport Medium available from Hyland Laboratories, Costa Mesa, California.

symptomatic patients and patients with a history of known sexual exposure regardless of symptoms or findings.

All patients with a presumptive diagnosis of gonorrhea are treated with doxycycline. Two 100 mg tablets are given in the clinic. In addition, the men are given envelopes with instructions to take doxycycline 100 mg tablets twice a day for three days. Women are given 100 mg tablets to take twice a day for five days. Patients are told to abstain from sexual intercourse to prevent reinfection while under treatment. Reports of the VDRL and bacteriologic studies are reviewed with the patient in one week. All are requested to return in three months for a second VDRL test.

Criteria for cure of gonorrhea have been established. Men who are asymptomatic on return in one week are considered cured. For women two negative smears and cultures a week apart are considered necessary for cure. If any initial report is positive, follow-up visits are scheduled until two consecutive weekly reports are entirely negative. Retreatment is instituted when necessary.

Each positive case is reported to the Los Angeles County Public Health Department as a communicable venereal disease. Case finding is then carried out by public health investigators.

Records of 490 patients attending the Torrance District Health Center Venereal Disease clinics from April to November 1969 were reviewed. Only patients with symptoms of gonorrhea or a history of exposure to gonorrhea were included in the study. Patients whose treatment had already been begun were excluded. Patients seen primarily for the diagnosis or therapy of syphilis were excluded.

A total of 226 patients received doxycycline for a presumptive diagnosis of gonorrhea and returned for follow-up in one week. These patients were the material of our study. One-hundred twenty-nine patients were males and 97 were females. Ninety-one percent were between 15 and 29 years of age. A previous history of gonorrhea was elicited from 51 males and females (27 percent of patients in the study). Only two males were asymptomatic. Seventy-five (77 percent) of the female patients were asymptomatic. None of the 226 patients had a positive VDRL test report.

The initial laboratory results of all patients in the study were compared (Table 1). All inconclusive reports were considered negative. The large number of symptomatic males with negative re-

TABLE 1.—Initial Laboratory Results in 226 Patients with a Presumptive Diagnosis of Gonorrhea

	Females	Males
<i>Symptomatic Patients</i>		
Positive for GC by smear, culture or both	11	64
Negative for GC by smear, and culture	11	63
<i>Asymptomatic Patients</i>		
Positive for GC by smear, culture or both	34	1
Negative for GC by smear, and culture	41	1
	97	129

TABLE 2.—Comparison of Smears and Cultures in Symptomatic Patients with Laboratory Evidence of Gonorrhea

	Females	Males
Smear positive }	5 (45%)	54 (84%)
Culture positive }		
Smear positive }	0	3 (5%)
Culture negative }		
Smear negative }	6 (55%)	7 (11%)
Culture positive }		
	11	64

TABLE 3.—Comparison of Smears and Cultures in Asymptomatic Females with Laboratory Evidence of Gonorrhea

Smear positive }	10 (30%)
Culture positive }	
Smear positive }	6 (18%)
Culture negative }	
Smear negative }	18 (52%)
Culture positive }	
	34

ports reflects the prevalence of non-specific urethritis seen in our area. A total of 110 patients had laboratory evidence of gonorrhea. A laboratory diagnosis by smear could be made for 89 percent of the men but only for 45 percent of the women in patients who were symptomatic (Table 2).

A laboratory diagnosis of gonorrhea in asymptomatic females could be made by smear in only 48 percent of cases (Table 3). The diagnosis doubled when the culture was also included. These findings were accentuated when smears and cultures in females with laboratory evidence of gonorrhea were compared (Table 4). More than

TABLE 4.—*Comparison of Smears and Cultures in All Female Patients with Laboratory Evidence of Gonorrhea*

	<i>Symptomatic</i>	<i>Asymptomatic</i>	<i>Total</i>
Smear negative } Culture positive }	5	10	15 (33%)
Smear positive } Culture negative }	0	6	6 (14%)
Smear negative } Culture positive }	6	18	24 (53%)
			45

TABLE 5.—*Results with Doxycycline in Patients with Laboratory Diagnosis of Gonorrhea*

	<i>Cures</i>	<i>Failures</i>	<i>% Cure</i>
Males	60	5	92
Females	43	2	96
	103	7	94

half of these women, whether symptomatic or not, could only be diagnosed by culture. The tables also show that in a few males (5 percent) and some females (14 percent) diagnosis can be made only by smear. Both smear and culture techniques are necessary to obtain confirming laboratory evidence of gonorrhea.

None of the patients whose bacteriological studies were negative on the initial visit, before treatment, had positive follow-up studies. There were seven treatment failures. The cure rate was 94 percent (Table 5). One man was given a second course of doxycycline and then did not return. The other six patients were treated with penicillin in aluminum monostearate in oil (PAM) 3.0 million units intramuscularly. Three (all men) did not return. The remaining man was asymptomatic with negative studies after PAM. Neither woman had been symptomatic. One was treated with PAM a second time before she was cured. The other had to be retreated three times (PAM, PAM, and doxycycline, and finally tetracycline alone) before she had negative laboratory studies.

Summary

Reasons for the alarming increase in the incidence of gonorrhea in the United States include problems in diagnosis and therapy. The physician who sees a patient with the possible diagnosis of gonorrhea is obligated to treat and follow the patient. In addition, he is obligated by law to report these cases to the local health authority so that

public health investigators can see that contacts receive medical attention.

The lack of symptoms in 75 percent of women known to have had contact with gonorrhea is particularly distressing. In both sexes, positive cultures with negative smears are often found. Occasionally, the opposite is true. However, even the best laboratory methods, used in complementary fashion—that is, both smears and cultures—yielded positive evidence in less than half of the patients treated for gonorrhea. Each patient who seeks medical care with a history of exposure to gonorrhea should be treated on the first visit without waiting for laboratory evidence. For both male and female patients, treatment should be based on history. Complete reliance on a laboratory diagnosis is not possible. Laboratory culture results are useful in confirming the diagnosis and evaluating a course of treatment. Antibiotic sensitivity results are not routinely obtained unless there are signs of resistance.

Treatment of gonorrhea, however, is no longer easy. The disease has shown varying susceptibility to penicillin in different geographical areas and the relative resistance of various strains has been steadily increasing, requiring higher dosage schedules for cure. Currently, the minimum dose of penicillin G injected intramuscularly is 4.8 million units in women and 2.4 million units in men. Benzathine penicillin is used in conjunction with the crystalline form. Benemid is of value in maintaining a high serum concentration.

Ampicillin, cephaloridine (Loridine®), kanamycin and carbenicillin represent other agents effective in the treatment of gonorrhea. Currently, the Los Angeles County Venereal Disease Center recommends tetracycline as the drug of choice. The patients seen in these centers are treated with the long-acting tetracycline, doxycycline. Therapy is begun with two 100 mg tablets administered under the watchful eye of a nurse. Treatment is continued with 100 mg twice a day for five days in women and three days in men.

We do not intend to imply that the therapeutic agent (doxycycline) and the dosage schedule give statistical advantage over other forms of tetracycline therapy. The suggested treatment schedule for the short-acting tetracycline is 2 grams to begin with and then 500 mg four times a day for five days in women and for three days in men. Erythromycin may be used in pregnancy or if there is allergic sensitivity to tetracycline. A course of

long-acting tetracyclines is two to three times as expensive as a course of the conventional 250 mg tetracycline capsules.

No amount of sophisticated laboratory diagnostic studies, new therapeutic measures, or increased case finding will eliminate gonorrhea. More attention must be placed on prophylaxis and on education of both the physician and the patient. Gonorrhea must be approached anew to make headway in its control.

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CORONARY CARE UNITS—FOR WHOM?

Should all patients with myocardial infarction be admitted to the coronary care unit—or just the seriously ill patients?

"Fifty-seven patients in a series reported by Melzer appeared to have mild myocardial infarction and were not admitted to the coronary care unit, but look what happened: 7 developed heart failure; 5 developed shock; there were 30 major arrhythmias, leading to 5 deaths. So we feel that *all* patients with myocardial infarction, even the good-risk patients, should go into a coronary care unit. There's just no doubt about it because we could save many of these patients in such a unit."

—ELIOT CORDAY, M.D., Los Angeles
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Changing Concepts on the Control of Growth Hormone Secretion in Man

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■ *New facts have emerged about growth hormone (HGH) secretion in man giving rise to new conceptions and to new questions.*

- *In well-nourished, lean human beings growth hormone is released in early deep sleep and the pattern of release observed from night to night is fairly constant.*

- *The release of growth hormone in sleep occurs when plasma glucose is not fluctuating and after insulin has fallen to a very low level. Plasma-free fatty acids may rise about two hours later but insulin does not rise in response to nocturnal HGH release.*

- *The releases of growth hormone in sleep appear to meet the needs for a physiological test for the study of problems of growth. Correlations of this test with the many pharmacologic maneuvers in current use for diagnosis remain to be made.*

- *Growth hormone secretion as judged by plasma concentrations relates to protein intake, such that protein depletion initiates compensatory elevation of plasma concentrations of growth hormone. Further elevations may occur with glucose loading—so-called “paradoxical” responses. In contrast, there is compensatory suppression of growth hormone secretion in obesity. Repletion of protein in the malnourished and reduction of weight in obesity cause return toward normal secretion of HGH.*

- *Levodopa as a possible specific stimulus to growth hormone release has just been reported and the implications of this finding for the child of short stature cannot yet be assessed.*

BEFORE ENTERING A DISCUSSION of the control of human growth hormone (HGH) secretion, it is probably important to state that “growth hormone” is the traditional name but that “somato-

trophin” has the advantage as a synonym in implying an action that continues throughout life rather than one restricted to the growing period. It is important to understand that an abundance of evidence points to the continuing secretion of growth hormone long after the growing period.

Two main views of action of growth hormone have existed. The first favors a direct, important action on protein metabolism which might re-

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sonably be called facilitation of protein synthesis. For example, the papers of Komer^{1,2} review extensive studies of direct effects of growth hormone on ribonucleic acid (RNA) synthesis and on the reading of the messenger RNA by ribosomes, which in turn synthesize protein.

The second main view has been that growth hormone facilitates protein synthesis by regulating carbohydrate and fat metabolism in such ways that protein synthesis, sometimes attributed largely to the action of insulin,³ can proceed with ample fuel and without diversion of amino acids to other needs. In the conception of the glucose fatty acid cycle⁴ it would appear that growth hormone induces lipolysis in adipose tissue and an increase in plasma concentrations of free fatty acid.⁵ The effect of the increase in free fatty acids is to suppress glucose utilization by muscle, one result being a tendency toward hyperglycemia and hence release of insulin. Although the development of this sequence is not timed for an obvious synergism of growth hormone and insulin, Rabinowitz and Zierler⁶ found that growth hormone and insulin have a synergistic effect on protein synthesis in their elegant experiments on forearm metabolism.

Stimulation of HGH Release

For many years growth hormone when injected in large quantities in adult animals has been found to be diabetogenic; and shortly after the major significance of plasma free fatty acids as fuel was first appreciated, growth hormone was shown to mobilize free fatty acids. Despite the importance of these observations the great impetus to recognition of metabolic determinants of the secretion of growth hormone came with the clear demonstration of Roth, Glick, Yalow and Berson⁷ of the role of hypoglycemia. Hypoglycemia, they showed, is a potent stimulus to growth hormone secretion in man as assessed by radioimmunoassay of growth hormone in plasma. Hypoglycemia must be severe if it is to be a reliable stimulus. The usual procedure is to inject intravenously 0.05 or 0.10 units of crystalline insulin per Kg of body weight and to consider the test adequate if either the 20- or 40-minute sample contains less than half the concentration of glucose of the pre-injection sample. The concentration of growth hormone is measured in these sam-

ples of plasma and at 60 and 90 minutes. That insulin itself does not stimulate growth hormone release is indicated by the observation that glucose infusion inhibits this effect of insulin.⁸

Arginine infusion has become a widely used method for stimulating secretion of growth hormone.⁹ The usual dosage is 30 grams of buffered Arginine-HCl, or 0.5 gm per Kg of body weight, infused over a 30-minute period. The procedure we have followed with ambulatory patients is to have them avoid both breakfast and exercise. In the out-patient department they lie still for a half hour. Then an "intracath" is inserted into an antecubital vein, a sample of venous blood is obtained, lightly heparinized, and it is labeled "minus 60." Normal saline solution is infused over the next 60 minutes and control samples are also collected at minus 30 minutes and at 0 time; for the next 30 minutes arginine is infused. Samples at 30, 60, 90, 120 and 180 minutes are also collected. The purpose of the pre-arginine sampling is to assure a low baseline; when this is done, most peak values occur 30 to 60 minutes after arginine injection is begun, although occasionally there is delay to 90 minutes. Rabinowitz et al¹⁰ found simultaneous glucose infusion not to suppress the rise in plasma HGH induced by arginine, but later these workers considered it to blunt the response.¹¹ Whereas one interpretation¹² is that arginine releases growth hormone because the hormone facilitates protein synthesis and so responds to the availability of the precursor, another interpretation is that arginine is a nonspecific stimulus.¹³ Since some patients experience nausea and even vomiting, one could invoke the stress phenomenon as the basis for growth hormone secretion, although presumably another basis would have to be found to explain the insulin release which also occurs with the infusion of arginine.

Exercise and "stress" have been recognized as causes for rises in plasma concentrations of HGH, and there have been standardizations of the former. How many of the tests which have been introduced for testing the capacity of the pituitary to release growth hormone should be classified nonspecific or stress would probably not be a matter of general agreement. The agents which have been presented as stimuli to HGH secretion include, in addition to the foregoing, pyrogen,¹⁴ vasopressin,¹⁵ glucagon,¹⁶ metyrapone,¹⁷ and corticotropin.¹⁸ It has become customary when in-

roducing a new agent for this purpose to present data on the effects of simultaneous administration of glucose.

In my opinion most of these agents have in common their tendency to cause nausea. Some agents which cause nausea facilitate transmission of impulses in the hypothalamus. Nausea is much more likely to develop when subjects are ambulatory than when at rest. Estrogens in large doses not only cause nausea but also have been recommended^{11,19} for testing male patients to enhance their releases of HGH in response to such agents as arginine. The doses of stilbesterol employed are from 5 to 10 mg daily for two days, but as much as 50 mg daily for a week or more has been administered to volunteers. This procedure was introduced because female patients after walking about while fasting were found to have higher plasma HGH concentrations than men.¹⁹

The relationship between estrogen and plasma growth hormone is a vexed one even in rats. Most evidence points toward lowering of pituitary concentrations of growth hormone by estrogen,²⁰ and lowered hormonal concentrations in the pituitary when the animal is in a steady state favor decreased secretion. Also favoring decreased secretion in female rats is its responsiveness to injected growth hormone. A good bioassay for growth hormone depends on the increase in body weight of female "plateaued" rats which follows injection of graded doses of the hormone. The male rat has both a larger concentration of growth hormone in the pituitary and is insensitive to injected growth hormone, the two facts fitting well with the idea that the male produces more growth hormone than the female. Nonetheless the female rat has been reported to have higher plasma concentrations of growth hormone than the male. Reservations on the significance of greater secretion of HGH in women than men after provocative tests may reasonably be held until there is certainty that the stimulus is physiological.

In the course of the investigations on the provocative stimuli to HGH secretion, it has become apparent that caution is required in interpreting low values in males, in the obese, after corticosteroids, and in hypothyroid subjects.^{12,21} In children who present with growth retardation which is more severe than the retardation of bone age, failure to induce a rise in HGH to 10 m μ g per ml probably warrants continuing investigation. Criteria differ for administration of HGH in therapy

of growth retardation, but it is clear, as in isolated deficiency of growth hormone, that detection of 2 and even 5 m μ g per ml²² is compatible with an excellent response in linear growth. Panhypopituitary subjects have even smaller or non-detectable amounts of HGH in plasma.

* * *

I have intended the foregoing discussion to be a preliminary summary, a description of some aspects of the "state of the art," against which the title "changing concepts" might be viewed, and I have sought to show that although many methods have been brought forward to test what responses the pituitary can make, there has remained substantial room for exploring the natural control of the secretion of growth hormone.

Release During Sleep

Quabbe et al²³ followed through on earlier observations by Hunter and Rigal on nocturnal rises in HGH²⁴ and found that during a 24-hour fast the peak of growth hormone concentration in plasma occurred during deep sleep. This clinical study has led to substantial and important investigations.^{25,26,27} Careful monitoring of sleep by polygraphic recording and insuring that sleep progresses in normal, uninterrupted cycles have proved essential to proper, interpretable studies of the release of growth hormone in sleep. To secure proper conditions of study we have a sound-proof, air-conditioned sleep room. At the head of the bed there is a console from which there is a cable to the EEG machine. Both this cable and tubing from the intracath enter the adjoining laboratory through a conduit in the wall separating the two rooms. Six leads are used—parietal, ocular and submandibular pairs. Despite the paraphernalia most patients fall asleep within five minutes of "lights out." Polygraphic tracings are made throughout the night and plasma is drawn at half-hour intervals or more frequently, the tubing being refilled with heparinized saline solution after each bleeding. Withdrawing blood at all vigorously results in clear disturbance of the polygraphic recording of sleep. This is brought out to emphasize the need for care and to make the point that any claim for a pharmacologic maneuver which is said to alter release of growth hormone should be supported by polygraphic evidence that sleep was not disturbed.

Before making polygraphically monitored studies, like Quabbe we studied glucose, insulin and growth hormone concentrations during behaviorally observed sleep.²⁸ In 16 normal, young, adult male volunteers, bled hourly, but resting and taking regular usual meals, growth hormone was easily detectable at only two times. Post eibal rises were observed in seven of 16 subjects, and the mean of the peak concentration was 8.3 nanograms per ml \pm 0.8. The second type of rise was both of greater magnitude and of more regular occurrence. In 14 of 16 subjects there was a rise of growth hormone concentration during early sleep to a mean of 17.2 nanograms per ml \pm 2.6 (standard error). In keeping with Quabbe's observations growth hormone was observed to rise at a time when glucose concentration was not varying detectably and insulin by radioimmunoassay was at or below 5 μ U per ml. Insulin was in very low concentration for at least two hours before the growth hormone peak and did not rise until the morning meal.

Polygraphic monitoring of human sleep has shown that normal sleep occurs in eyes with progression from Stage I down to Stages III and IV, which are defined by percentage of time dominated by slow wave eyes (sws), a return from prominent sws, with a period of rapid eye movement (REM) or paradoxical sleep completing the eye. The studies cited relate growth hormone release to sws and show the major release commonly to occur in the first eye.

We now appear to have releases of growth hormone during the waking hours, and although these have been grouped either as metabolically determined or as stress induced, the distinctions seem more blurred than clear. The sleep release of growth hormone is a second type, and it appears to be neurally determined rather than metabolically. In support of this statement are the observations on sleep deprivation.²⁹ Subjects kept awake all night although at complete rest in a darkened room had no release of growth hormone. That they were awake was shown by polygraphic monitoring. However, when they fell asleep the morning following a night of sleep deprivation the sleep release of growth hormone occurred promptly.

Preliminary indications are that allowing an individual to sleep but preventing entry into sws by applying an electric stimulus not powerful enough to awaken him will prevent the sleep re-

lease of growth hormone.³⁰ The release of growth hormone in sleep is not altered by significant hyperglycemia effected by infusing glucose intravenously in the sleeping subject.²⁸ In the normal sleeping subject the release of growth hormone occurs independently of the blood sugar and of the insulin concentration in plasma. Thus in normal sleep the release of growth hormone occurs while there is minimal fluctuation in the blood sugar and while insulin is hardly detectable or non-detectable by radioimmunoassay, and this release also occurs despite induction of hyperglycemia and its consequent rise in insulin concentrations. Diabetic persons experience the sleep release of growth hormone despite hyperglycemia, and their concentrations of growth hormone in plasma are not remarkable.³¹

Normal vs Abnormal Secretion

Glik, Roth, Yalow and Berson³² pointed out that it is extremely difficult to prove that hyperglycemia suppresses the concentration of growth hormone in plasma. This is because the concentration in the relaxed, resting volunteer is just at the level of detectability. Nonetheless, although the effect of hyperglycemia in suppressing growth hormone may be less specific than originally thought, glucose infusion does appear to be clinically useful in the evaluation of acromegaly. Failure during a standard glucose tolerance test of growth hormone concentrations in plasma to fall below 5 nanograms per ml may be considered textbook evidence of acromegaly. In my opinion it is very important in applying this test that clinical features of the disease be present, and I urge that repeated determinations of HGH be made with the subject at rest. A continuing overproduction of growth hormone as indicated by repeated demonstrations of elevated plasma HGH throughout the day should be observed as well as failure of glucose loading to suppress HGH in plasma to low levels. An important study by Lawrence et al³³ suggests that acromegaly is a hypothalamic disease, with adenoma formation probably a late event, and that "paradoxical" responses to glucose loading, exercise, insulin, or arginine were the rule in active acromegaly. With one or another of the tests there strongly tends to be an abnormal response.

There are several reasons for advising caution in using a single glucose tolerance test with

plasma HGH measurements as the sole diagnostic measure for acromegaly. According to the work of Rayyis and Bethune,³⁴ hyperglycemia suppresses ACTH—even in Addison's disease—so that the suppression of growth hormone by glucose infusion may be considered somewhat nonspecific. Further, there are numerous reports of so-called "paradoxical" release of growth hormone by glucose loading apart from acromegaly.^{35,36,37,28} Finally, the major facts about acromegaly make life difficult for patient and physician alike. Thus, in a rare disease such as acromegaly, where early diagnosis is important if the physical ravages of the disease are to be avoided, and where treatment is drastic if it is to be effective, opportunities for serious error abound. Many more patients may have to be evaluated for the x-ray finding of a sella turcica at the upper limit of normal size than will prove to have acromegaly. The determination of growth hormone in plasma is a signal advance in the diagnosis of acromegaly, but the earlier the diagnosis, the greater the need for caution in the interpretation of data on growth hormone concentrations. This is especially true because conventional x-ray treatment is usually unsatisfactory and more effective measures must be utilized.

Relation to Nutrition

I alluded to "paradoxical" release of growth hormone following glucose loading. I should point out that this is an appropriate term only if one is convinced that the normal rules governing growth hormone release are well in hand. Actually an understanding of the rules appears still to be evolving, and it may be helpful at this time to consider release of growth hormone in reference to the nutritional state, probably the most interesting and important facet of the whole problem.

Sims and Horton³⁸ studied growth hormone secretion in volunteers in Vermont State Prison who force-fed themselves and achieved an average increment of weight gain to 26 percent over their initial lean weight. They observed a "progressive impairment" of the rise in plasma growth hormone that, as already mentioned, tends to occur 4 to 6 hours after meals. They also observed pronounced decrease in nocturnal elevations of growth hormone plasma levels in these subjects. These observers contrasted their findings with

those of Pimstone and co-workers^{39,40} that kwashiorkor patients have elevated plasma concentrations of growth hormone which returned to normal with protein repletion. In well controlled studies a striking fall in HGH concentrations was observed after only three days of protein repletion; the fall was from a mean of 24 nanograms per ml to 10 ng per ml. Continuing the high protein intake caused further lowering of the basal morning concentrations of HGH in plasma. The secretory mechanism for growth hormone appeared highly sensitive to the state of protein nutrition, and Pimstone et al made certain it was indeed the protein, not just calories, that lowered basal concentrations of HGH. Glick et al³² and Marks and Howorth⁴¹ observed that elevated plasma HGH occurs in some patients with anorexia nervosa, and Landon et al,⁴² noting failure of insulin hypoglycemia to evoke the expected rise in HGH in two of five patients with anorexia nervosa, suggested this related to the high resting levels. Failure of plasma cortisol concentrations to rise after insulin hypoglycemia in some of their patients with anorexia nervosa was also thought to be related in part to high resting levels.

In an extension of these observations we²⁸ noted that in eight of ten patients with anorexia nervosa glucose loading led to a prompt and major rise in the plasma concentration of HGH, and in many instances the concentration of HGH reached its maximum before the peak in immunoreactive insulin occurred. In this group of malnourished subjects glucose loading, therefore, frequently stimulated growth hormone secretion, and we offered as a working hypothesis that the release of growth hormone is governed by a highly sophisticated sensor, well aware of the nutritional needs of the body. It appears that this sensor is the brain itself.

Because even the most recent textbooks do not present growth hormone as having a significant function in the adaptation to malnutrition, one of the world's most threatening problems, it appears worthwhile to press the case for the evidence that does exist on this score. If the result is to stimulate further inquiry, that will suffice. In my view the best interpretation of the data at hand is that growth hormone secretion adapts to the nutritional state and that the controls are such that in protein malnutrition growth hormone synthesis is selectively favored and in turn

it promotes synthesis of vital proteins. The complexity of controls is indicated by the hypoalbuminemia of kwashiorkor which develops presumably because of depression of albumin synthesis by the liver while vital hepatic enzymes are maintained. In groping for the rules for growth hormone secretion I take note of the fact that in starving adults at rest about 20 percent of caloric need is met by protein breakdown; the sudden availability of calories in the form of a glucose load presents an opportunity for reversing this breakdown and the release of growth hormone can be held to favor renewed synthesis.

Commenting on therapeutic responses, Daughaday¹² noted that "growth hormone seems to affect the central nervous system directly or indirectly, in that pituitary dwarfs become much more active and alert," and this has been our repeated experience. It becomes intriguing speculation to explain the release of growth hormone early in (deep) sleep as serving the needs of the brain itself for facilitation of protein synthesis. There is no experimental evidence for such an hypothesis, although a great amount of research demonstrates the brain to be highly active in the synthesis of new protein. The hypothesis requires growth hormone to enter the brain rather than being excluded by a "blood-brain barrier."

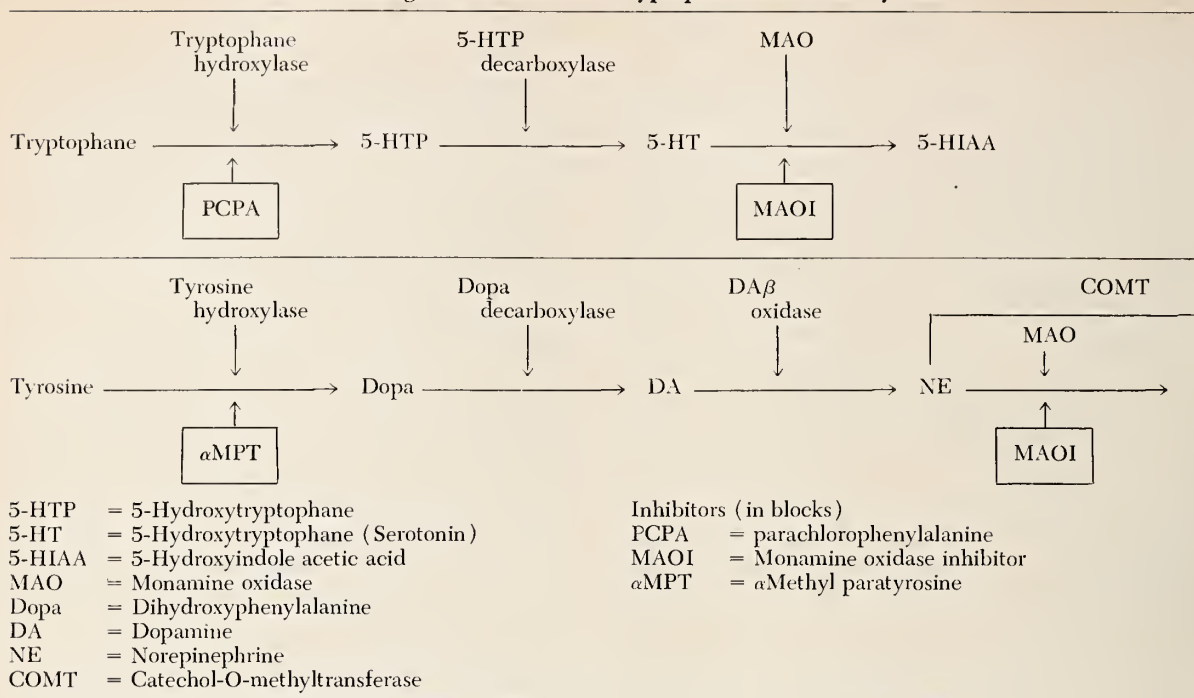
To recapitulate, the major release of growth hormone which is regularly observed under physiological conditions in well nourished subjects of normal body weight occurs in sleep. The sleep release of growth hormone was timed by astute bedside observation with deep sleep, and polygraphic studies have repeatedly confirmed this. Hyperglycemia does not suppress this release. Nutritional aspects of the release of growth hormone in sleep have not been well studied, but Sims and Horton³⁸ offered preliminary data suggesting that forced feeding with resultant obesity suppresses nocturnal releases of HGH, presumably in sleep. Numerous observations indicate blunted HGH releases in obesity to such stimuli as hypoglycemia and arginine, and Londono et al¹³ have shown that as obesity is corrected there is a progressive return toward the normal release of HGH in response to insulin-induced hypoglycemia. In contrast to the sluggish secretion of HGH in the obese and to the nocturnal secretion of growth hormone in the normal subjects, is the hypersecretion of HGH in malnutrition. This hypersecretion is observed in the daytime and under basal

conditions; our finding that glucose loading actually stimulates HGH secretion in anorexia nervosa led us to suggest that when malnutrition is severe, glucose ingestion may represent an opportunity for diverting amino acids from gluconeogenesis to protein synthesis and that growth hormone is released to facilitate this process.

The logical conclusion from the data on growth hormone secretion and nutritional state is that the obese are less in need of growth hormone than the lean. Support for this conclusion would come from observations that force-fed children would grow despite undoubted deficiency of HGH. Just such data have been provided in studies of hypopituitary children selected because of insatiable appetites and resultant obesity following neurosurgical removal of craniopharyngioma.⁴⁴ Despite absence of growth hormone from plasma or very low concentrations consistent with total or subtotal removal of the pituitary, "catch-up" growth was observed in this select group, and the growth rate tended to parallel the degree of hyperphagia. In these hyperphagic persons with normal growth rates despite pituitary destruction the plasma HGH concentrations were indeed low and no greater than those of the children with growth failure due to selective HGH deficiency as described from their extensive experience by Goodman, Grumbach and Kaplan.⁴⁵

There is opportunity to consider the high secretion of growth hormone in malnutrition, including "paradoxical" elevation after glucose loading in comparison with acromegaly. Reference has been made to the work of Lawrence et al,³³ who observed that paradoxical or abnormal responses of HGH release in acromegaly after a variety of stimuli were the rule. From these observations they suggested that acromegaly is a hypothalamic disease. Looking at the available data on the high rate of HGH secretion in malnutrition and the paradoxical responses, I am led to suggest that acromegaly is a disease in which the brain perceives the individual as malnourished. At the practical level this suggestion does not lead to action in respect to acromegaly, but it does serve to reinforce the need for studying the effects of glucose loading on growth hormone secretion in marginal and in severe protein malnutrition. From a careful study which should include observations in protein repletion, a test for malnutrition might emerge.

Chart 1.—Biogenic amines from Tryptophane and from Tyrosine



Relation to the Bioamines

A very recent study¹⁶ relates growth hormone release to the administration of levodopa. In patients with parkinsonism studied three days after medication was begun, Boyd and his colleagues found the oral administration of a single dose of levodopa to stimulate growth hormone release with resulting plasma concentrations as high as 20 and 30 nanograms per ml. As little as 0.5 gram was effective in the near-absence of side effects, including nausea. At least as significant was the observation that after six months of therapy with levodopa patients with parkinsonism responded to the same dose with a rise in plasma HGH of equal magnitude. It was also noted that hyperglycemia did not suppress this effect of levodopa. If these observations apply to normal subjects an important therapeutic opportunity may have been opened. First it will be helpful to learn whether levodopa is any more specific than the stimuli already in use, particularly since levodopa in 1.0 and 1.5 gram doses causes nausea. Levodopa is able to cross the blood-brain barrier, unlike the biogenic amines, dopamine, norepinephrine and serotonin. Parenthetically, epinephrine itself is practically or completely absent from the central nervous system. A second

and important consideration is that levodopa could act to release growth hormone and so enhance the growth rate. A single bedtime dose might prove an answer to a small child's prayer.

It may be appropriate at this time to review briefly the precursors of norepinephrine and of serotonin. Tryptophane is converted to 5-hydroxytryptamine by tryptamine hydroxylase and the amine is decarboxylated to form serotonin (5-HT) as shown in Chart 1. The precursor for norepinephrine (NE) is tyrosine which is converted by a series of enzymatic reactions to dopa, dopamine, and then to NE. The degradative steps involve the enzyme monoamine oxidase (MAO) which deaminates serotonin to yield 5-hydroxyindoleacetic acid (5-HIAA). MAO also catabolizes dopa, and NE is catabolized both by MAO and catechol-O-methyltransferase. Parachlorophenylalanine inhibits tryptophan hydroxylase, decreasing serotonin, and alpha-methyl paratyrosine suppresses dopa formation by tyrosine hydroxylase. The finding that levodopa stimulates growth hormone secretion in parkinsonism would appear to justify brief reference to studies in animals on the biogenic amines in an attempt to relate sleep with serotonin, dopamine, and norepinephrine and so the metabolism of these substances with release of growth hormone.

It has long been known from the work of Vogt¹⁷ that the central nervous system is rich in norepinephrine. Fuxe and Hokfelt¹⁸ after an extensive anatomical review of the localization of specific biogenic amines in the central nervous system noted that giving dopa leads to facilitation of catecholamine mediated transmission, and apomorphine selectively stimulates dopamine receptors in the brain. Dopamine is thought to act as a transmitter substance in the median eminence, and they suggest the endocrine activity of apomorphine (known to release corticotropin) deserves study. With its well known emetic effects, especially in ambulatory subjects, apomorphine may also prove to be a releaser of HGH. It should be noted, too, that androgens, estrogens and castration all have effects on anterior hypothalamic concentrations of norepinephrine.

Weitzman,⁴⁹ reviewing biogenic amines and sleep stage activity, puts to rest the hypothesis that in waking a toxin accumulates in the blood which is cleared in sleep, noting that in Siamese twins with common circulation, independent sleep-waking activity was observed. Current theory focuses on the biogenic amines, and their metabolism is related to sleeping and waking states. In monkeys when tyrosine hydroxylase is inhibited by alpha methyl paratyrosine, decreasing dopa and therefore dopamine concentrations, there is an increase in non-rapid eye movement (REM) sleep time but a decrease in REM sleep time, and the monkeys exhibit less aggressive behavior. When the specific inhibitor of tryptophan hydroxylase, parachlorophenylalanine, was given to monkeys with resultant serotonin depletion there was a decrease in Stages 3 and 4 sleep with little effect on REM sleep.

In cats the effects of parachlorophenylalanine are more striking. According to Jouvet, this drug has no effect for 24 hours, after which there is more than a day of total insomnia, as determined behaviorally and by EEG. Sleep does not return fully to normal for 100 hours from the time of injection. Jouvet studied effects of this drug by giving 5-hydroxytryptophan as a second injection during the stage of insomnia. The temporary effect of the second drug is to allow, in a few minutes, recovery from insomnia with normal REM and non-REM sleep. The experiment speaks for a major role of the biogenic amine, serotonin, on sleep. Unfortunately it does not help us clarify the relationship between sleep and HGH release on

the one hand and levodopa and HGH release on the other. The patterns of sleep in different species vary so greatly that it seems reasonable to expect different chemical mediation in the central nervous system. In human studies it is clear that MAO inhibitors and reserpine, which depletes dopamine, norepinephrine and serotonin, do alter the sleep-time in differing stages of sleep. Reserpine and monamine oxidase inhibitors substantially alter sleep patterns in animals and much may be learned from animal studies combined with radio-immunoassays for growth hormone. According to Jouvet⁵⁰ it is important that REM sleep ends the sleep cycle. In narcolepsy and cataplexy REM sleep follows wakefulness, and these states may be informative in regard to sleep release of HGH. Similarly in parkinsonism the substantia nigra is depleted of dopamine⁵¹ and studies of sleep and HGH release before and after levodopa treatment may prove of interest. We attempted to study hydrancephaly in which there are no brain waves—children legally dead if recently proposed criteria were adopted—and could find no rhythm in HGH in plasma.²⁸ We also failed to stimulate growth hormone secretion in man by ether infusion.⁵²

In regard to certain stimuli in man, alpha adrenergic blockers suppress growth hormone release^{53,54,55} and such beta adrenergic blocking agents as propanolol⁵⁶ enhance its secretion. There is an obvious need for sleep studies in respect to these agents and the release of HGH.

That the secretion of human growth hormone by the pituitary gland may have a further mediator, growth hormone releasing factor, is highly likely but awaits proof. At present only thyrotropin releasing factor has been structurally characterized.

In regard to the release of human growth hormone in sleep much remains to be done, but the circumstantial evidence for a paramount role in this release by sleep which involves catecholamine and serotonin metabolism appears strong. Growth hormone appears to play a role in protein synthesis and it seems no longer necessary to confine it to the role of a relatively minor regulator of carbohydrate and fatty acid metabolism. On the other hand, whether release of growth hormone in sleep is to be conceived of as an innate rhythm or as a mechanism serving the need of the brain itself for facilitation of protein synthesis is speculative.

The conception of regulation of growth hormone by changes in concentration in blood sugar stimulated an enormous amount of productive work, and it can be expected that new insights will come from continuing studies of the control of growth hormone secretion in man.

The mechanisms stimulating growth hormone secretion during waking hours have been mainly grouped as stress responses, and I have emphasized the particular factor of nausea. The whole concept of stress was an outgrowth of the "flight or fight" conceptions of Cannon, and the role of growth hormone as one of many modulating influences on metabolism in times of great exertion or crisis may well have had survival value in the evolutionary sense. The sleep release of growth hormone seems to make physiological sense⁶⁷ with regard to protein synthesis, including growth itself.

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Specialty Conference

Syphilis

Discussants: JAMES N. MILLER, PH.D., JAMES R. NELSON, M.D.,
RONALD M. REISNER, M.D., AND JERROLD A. TURNER, M.D.

This is the transcription of the regular teaching conferences in Infectious Diseases held weekly at Harbor General Hospital, Torrance. The transcription was edited by Drs. Jerrold Turner, Irwin Ziment and Lucien B. Guze.

JERROLD A. TURNER, M.D.* Syphilis appeared in epidemic form in Europe during the sixteenth and seventeenth centuries. Until the twentieth century it continued to be prevalent among the lower socio-economic groups and was a plague of armies during military campaigns. It was only with the introduction of penicillin therapy in the 1940's that the incidence of primary and secondary syphilis declined sharply. The low point in reported cases, which was reached in the mid 1950's, was quickly followed by reductions in financial support for venereal disease control and research programs. Many medical students were graduated without ever having seen a syphilitic lesion and with little formal instruction on clinical syphilis. Then the downward trend in the incidence of infectious syphilis rapidly reversed itself and venereal disease again reached epidemic proportions during the 1960's.

The need to increase the awareness of the medical community and provide the practicing physician with current information on the diagnosis and management of syphilis is apparent.

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This symposium was planned to survey the important and practical aspects of clinical syphilis. Dr. Ronald Reisner will begin by reviewing the natural history of the disease and will discuss the most important features in the recognition of syphilis, the visible lesions. Our complacency about the penicillin cure of all forms of syphilis will be disturbed by Dr. James Nelson's discussion of progressive neurosyphilis despite penicillin therapy, and Dr. James Miller will present a practical approach to the serodiagnosis of syphilis and the interpretation of serologic tests in problem cases.

Natural History and Cutaneous Manifestations

Ronald M. Reisner, M.D.:* An appreciation of the natural history of untreated syphilis is essential to intelligent management of the disease. Information is available as a result of the unique Oslo experience based upon the period 1891 to 1910 when Boeck in Norway treated 1,978 patients with primary or secondary syphilis solely by keeping patients in hospital for community protection until all traces of the disease had disappeared. Drawing on this large reservoir of

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untreated patients, Bruusgaard in 1929, and later Gjestland in the years 1948 through 1951, traced these patients and ultimately obtained clinical information on 1,147.¹ The most important findings in this study are summarized as follows.

Approximately two-thirds of all untreated infected persons live out their lives with little or no physical inconvenience, although more than half of them will have a persistent positive serologic reaction throughout life. In approximately one-third of untreated syphilitic patients significant destructive lesions will develop. These include central nervous system syphilis in 8 percent of patients, cardiovascular syphilis in 10 percent and late benign mucocutaneous-osseous syphilis in 17 percent. Almost one-quarter of the entire group of untreated patients can be expected to die primarily as a result of syphilis—80 percent of them from cardiovascular complications and most of the remaining 20 percent from central nervous system complications.

As important as this information is from a prognostic point of view, perhaps even more important from the public health point of view are the startling facts which were revealed concerning the problem of clinical secondary relapse. This can be defined as a recrudescence of the signs and symptoms of secondary syphilis in patients in whom all apparent clinical symptoms and signs have previously disappeared. Since secondary syphilis is highly infectious, this becomes a very significant factor in prolonging the period of potential infectiousness of any given patient. About one-quarter of all patients with untreated syphilis had one or more relapses. More than two-thirds of Boeck's patients experienced all their relapses within six months; but some of the remaining one-third had relapses as long as five years after the time of infection. Since about 85 percent of these relapses involved the mouth, throat or anogenital area, this meant that any given patient might conceivably serve as an active reservoir of infection for as long as five years after initial infection, if untreated. Hence diagnosis and treatment of syphilis during the highly contagious primary and secondary stages is desirable not only to protect the patient against late destructive sequelae, but also very importantly from the public health point of view.

The etiologic agent of syphilis is *Treponema pallidum*, a delicate spirochete, 6 to 15 microns in length, about 0.25 microns in diameter and usually containing between 6 and 14 spirals. Its

characteristic motility under the darkfield microscope is an important criterion for its differentiation from other spirochetes; however, at times it is impossible to differentiate *T. pallidum* from these other organisms by microscopy.

Outside the host, *T. pallidum* is very sensitive to a variety of agents such as heat, drying, and soap and water, all of which kill it promptly. In animal experiments it has proven to be a very potent pathogen, with the minimal dose required to infect a rabbit being a single treponeme of the pathogenic Nichols strain intratesticularly, or four treponemes if the inoculation is intradermal.

For all practical purposes syphilis is transmitted by direct contact with an infectious lesion. The organism will pass through abraded skin or through intact mucous membrane. The infection becomes systemic within a very few hours after inoculation, although clinical and serologic signs do not appear until later. The events occurring following initial infection can be summarized by stages in the natural history: Incubation; primary syphilis; secondary syphilis; latent syphilis; and late syphilis.

- **Incubation period:** Nine to 90 days (usually three to four weeks) after *T. pallidum* has entered the host, there occurs at the site of entry the primary lesion—the chancre.

- **Primary syphilis:** The elementary lesion of primary syphilis is the chancre, which is usually a firm indurated papule with an ulcerated or crusted surface varying in size from 2 mm to 2 cm. It is usually single and painless, but may be multiple and may be painful if secondarily infected with other organisms. Extragenital chancres may also be painful and are usually accompanied, as are genital chancres, by regional adenopathy. The involved nodes are usually firm, moveable and non-tender. In males chancres are commonly located on the penis and thus are usually clinically apparent, whereas in women they are frequently within the vagina or on the cervix and therefore more likely to escape clinical detection. Extragenital lesions may involve any portion of the body; common areas are the lips, tongue, nipple, fingers, and anus—the latter site increasingly recognized owing to homosexual transmission.

Since the chancre heals spontaneously in four to six weeks, unless the diagnosis is suspected the disappearance of the lesion may be attributed to whatever antibacterial or other agent may have been used topically. If a lesion is

suspected of being a luetic chancre, the diagnosis may be confirmed by darkfield examination of exudate from the lesion or of aspirate from enlarged regional nodes. Darkfield examination takes skill and experience to perform and interpret, and as a practical matter is frequently not readily available to a physician in his office.

Within a month after the appearance of the chancre, the overwhelming majority of patients with primary syphilis will have positive serologic reaction. However, early in the course of the chancre, the result of a serologic test may be negative. It is important to be aware of this and to perform repeat studies lest the diagnosis be missed. A convenient rule of thumb which, while not precisely accurate, serves as a practical guide, is: About 25 percent of patients with primary lesions of syphilis will have positive serologic reaction after the chancre has been present for one week, 50 percent at the end of two weeks, 75 percent at the end of three weeks and approximately 100 percent at the end of four weeks. The problems of which serologic tests to use, when to use them and how to interpret will be discussed later by Dr. Miller.

Among the diseases to be considered in the differential diagnosis are chancroid, granuloma inguinale, lymphogranuloma venereum, herpes progenitalis, carcinoma, scabies, trauma, lichen planus, psoriasis, drug eruptions, aphthosis, systemic fungus infections and Reiter's syndrome. Without going into detail, it may be said generally that the clinical findings and the history of the natural course of the disease will help rule in or rule out most of these differential possibilities. It is important to remember that other infections may co-exist with syphilis, especially other venereal diseases and most especially chancroid. False positive serologic tests may occur with chancroid and lymphogranuloma venereum, further confusing the picture. However, the demonstration of *Hemophilus ducreyi* by direct stain of a smear or by culture in the case of chancroid, and the demonstration of rising complement fixation titers in the case of lymphogranuloma venereum coupled with the history and physical findings will usually resolve the problem.

• **Secondary Syphilis:** The lesions of secondary syphilis may appear any time from two to ten weeks after the appearance of the chancre, although at times the interval between the onset of the chancre and the onset of the secondary

manifestations of syphilis may be as long as months. Since the chancre may last up to six weeks, it is obvious that in some patients the manifestations of secondary syphilis will appear while the chancre is still present. The individual episode of secondary syphilis usually lasts about two to six weeks.

Secondary syphilis is truly the "great imitator." It may involve any organ in the body and any cutaneous or mucosal surface. The diagnosis of secondary syphilis, however, is ordinarily suspected predominantly because of the appearance of skin and mucous membrane lesions. Skin lesions are usually dry and very rarely itchy. Vesiculo-bullous lesions are not seen in syphilis of adults, although they may occur in congenital syphilis in the newborn. With these qualifications in mind, secondary syphilis may mimic almost any kind of skin lesion found in other cutaneous diseases—most particularly macular, papular, follicular, papulosquamous and pustular lesions. They are usually bilaterally symmetrical except in relapsing secondary syphilis, where they may be asymmetrical and tend to be arciform.

Patchy scalp-hair loss, often described as "moth-eaten" and often beginning on the occipital scalp, is a common finding in secondary syphilis. Less common is loss of the lateral third of the eyebrow and loss of eyelashes.

In areas of the body where moisture is present, usually in the anogenital region, condylomata lata, which are smooth, flat, sessile, moist papules, may occur. Mucous membrane lesions may occur in the mouth, throat and cervix. These take the appearance of red, eroded areas with a white membranous surface and are known as mucous patches. These moist cutaneous and mucous membrane lesions contain large numbers of spirochetes and are highly infectious.

An important clinical finding in secondary syphilis is the presence of general lymphadenopathy. In addition, a variety of constitutional symptoms including fever and malaise may be found.

Even when facilities are available, successful darkfield examination of the lesions of secondary syphilis is difficult to achieve, in part due to the ease with which the organism may be destroyed by contact with soap, topical antiseptics and the like which may have been applied to the lesions, and in part because the lesions from which *T. pallidum* is most readily recovered are

the mucous membrane lesions, and here differentiation from saprophytic treponemes normally found in the area may be impossible.

The differential diagnosis of the muco-cutaneous lesions of secondary syphilis would encompass a major part of a textbook of dermatology. Certain conditions, however, must be considered more carefully:

Condylomata Acuminata • These are ordinary viral warts which assume their peculiar acuminate or conical shape in any moist area, but most particularly in the ano-genital region. Their configuration contrasts with the flat-topped, button-like sessile condylomata lata. Darkfield examination may be confusing in that large numbers of saprophytic treponemes may be observed in scrapings from condylomata acuminata; however, the serologic tests for syphilis are negative.

Infectious Mononucleosis • Differentiation of infectious mononucleosis from secondary syphilis may be very difficult at times, particularly in the presence of a biologically false positive serologic reaction coupled with a generalized eruption, fever, malaise and lymphadenopathy. The findings for infectious mononucleosis including atypical lymphocytes in the peripheral blood and positive heterophile agglutination tests help differentiate the two diseases.

Pityriasis Rosea • This is a maculosquamous or papulosquamous erythematous eruption with lesions tending to occur along the lines of cleavage, usually sparing the distal extremities, head, neck and mucous membranes, and often preceded for days to a week or more by an isolated lesion known as the herald patch.

Other Papulosquamous Eruptions • Psoriasis, lichen planus, and tinea versicolor can usually be distinguished on the grounds of clinical appearance and their more prolonged course.

Drug Eruptions • Drug eruptions, like secondary syphilis, are the great imitators of cutaneous disease. Appropriate history coupled with a negative serologic reaction will ordinarily make it possible to distinguish between these two proctean diseases.

• **Latent Syphilis:** Latent syphilis is the stage at which no clinical signs or symptoms of the disease are present, the spinal fluid serologic reaction is negative, and serum serologic tests for syphilis are positive. The diagnosis is made on the basis of positive non-treponemal serologic tests for syphilis confirmed by positive treponemal tests. Confirmatory historical evidence of primary or

secondary syphilis or changes in serologic reaction from negative to positive are desirable but often unobtainable.

Syphilis which has been present for four years or more is seldom transmissible except in the case of transplacental transmission: the fetus may become infected regardless of the duration of the untreated disease in the mother. If spinal fluid examinations are still normal four or more years after the onset of infection, the likelihood of subsequent development of neurosyphilis becomes extremely small. Based on these criteria, particularly that of potential communicability, latent syphilis is often divided into early and late phases. For the reasons noted above, this division is often taken at four years after the onset of infection, although some authorities use one year for epidemiologic purposes.

• **Late Syphilis:** Late syphilis, like early syphilis, is a disease whose primary target is the blood vessel. The one exception to this is the gumma, which is probably a hyperimmune process. Except for gummas, an obliterative endarteritis of small arteries and arterioles resulting in inflammatory and necrotic changes is responsible for the clinical lesions of late syphilis.

Late syphilis differs broadly from early syphilis in its lack of infectivity (except in pregnant women), negative darkfield findings, its destructive rather than non-destructive lesions, and its relatively stable often low-titered Standard Serologic Tests for syphilis, which change little even after therapy. Only a very brief review of significant mucocutaneous manifestations will be undertaken at this point. It should be remembered that involvement of one system does not protect against involvement of another, and a thorough study of the patient must be undertaken with particular attention to the cardiovascular and central nervous system.

The significant mucocutaneous lesion of late syphilis is the gumma. The organs most commonly involved in gumma formation are the skin, bones and liver, but almost any organ may be involved. On the skin, gummas may be either single or multiple and ordinarily they tend to form circular or arciform chronic lesions which are destructive, producing ulceration, scarring and sometimes perforation. The lesions tend to extend peripherally and heal centrally. In gummatous syphilis the serologic tests are almost always reactive and ordinarily are of high titer. Mucocuta-

neous gummas may mimic any of a number of destructive diseases, particularly the granulomatous and neoplastic diseases from which they may be differentiated by biopsy.

Treatment

Jerrold A. Turner, M.D.: Resistance of *T. pallidum* to penicillin has not been demonstrated or induced in the laboratory and there are no present indications, with the exception of the unique conditions cited by Dr. Nelson, for altering accepted regimens of penicillin therapy. Table 1 summarizes the recommendations of the United States Public Health Service.²

Treatment of syphilis with oral penicillin should not be attempted because of the unpredictability of absorption and the possible unreliability of the patient. When penicillin is contraindicated, demethylchlortetracycline in a total dose of 30 grams or erythromycin or tetracycline in a total dose of 40 grams may be used to treat early syphilis. These antibiotics should be given four times daily in equally divided doses over 15 days. When using either erythromycin, demethylchlortetracycline or tetracycline, the patient must be followed closely, and spinal fluid examination is recommended before final discharge. The treatment of late syphilis, cardiovascular or neurosyphilis, requires doubling the dose of oral antibiotic. Tetracycline may produce permanent discoloration of developing teeth and its use should be avoided during pregnancy and in children under 12 years of age. The physician should be aware of the tendency for demethylchlortetracycline to induce photosensitive skin eruptions.

Adequate antibiotic therapy, either with penicillin or alternate drugs, will not bring about resolution of the interstitial keratitis of congenital syphilis. Consultation with an ophthalmologist is necessary. Appropriate immediate therapy for the manifestations of decompensated cardiovascular syphilis always should take precedence over specific treatment with penicillin or other antibiotics.

During the therapy of syphilis, there may be an exacerbation of local lesions, accompanied by fever. This response, called the Jarisch-Herxheimer reaction, is attributed to the release of antigenic material from lysis of the treponemes. Symptoms usually occur within 12 hours of commencing treatment and rarely persist longer than 24 hours. The reaction is more frequent and most

pronounced in primary and secondary syphilis. Symptomatic treatment of the reaction is all that is required. The appearance of this reaction is no indication for stopping therapy.

Progressive Neurosyphilis Despite Penicillin Therapy

James R. Nelson, M.D.:^{*} This presentation will focus on the management of adult patients presenting with the late manifestations of syphilis, particularly congenitally acquired infection. Although the early treatment of maternal syphilis has drastically reduced the incidence of active fetal infection from about 95 percent to less than 5 percent, the late manifestations of the disease are not entirely prevented by treatment in the latter months of pregnancy. There has been a steady increase in the incidence of congenital syphilis in the United States to at least four or five thousand cases a year. The manifestations of congenital syphilis were reviewed recently by Robinson,³ who considers the clinically characteristic type of interstitial keratitis, mulberry molars and serrated incisors (Hutchinson's teeth) as the only pathognomonic signs of congenital syphilis; he looks upon other classical findings, such as frontal bossing, saber shins, saddle nose, high arches, rhagades (circumoral radiating scars), painful hydrarthrosis (Clutton's joints) and other signs, as suggestive of congenital syphilis but not specific. The most interesting manifestations of congenital syphilis are the delayed late inflammatory symptoms of interstitial keratitis, joint inflammation and progressive inner ear destruction with hearing loss and vertigo. The otologic changes may also occur long after acquired syphilis has been treated. In contrast to the very rare degenerative changes seen after other bacterial infections of the nervous system, the occurrence of progressive nervous system damage in several patients who allegedly were either "cured" by earlier high dose penicillin therapy or were "sero-fast" (presumably had arrested disease), has been extremely puzzling. Our experience with otologic involvement has been most instructive, particularly because some patients have apparently benefited from treatment with cortisone alone or in combination with very high doses of penicillin derivatives. Specifically, we have been faced with six young

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TABLE 1.—Treatment of Syphilis

Stage		Treatment			Follow-up with Quantitative Serologic Tests
		Aqueous Procaine Penicillin G	Procaine Penicillin G in Aluminum Monostearate	Benzathine Penicillin G	
Primary and Secondary		600,000 units daily for 8 days (total dose 4.8 million units)	2.4 million units first dose followed by 2 doses of 1.2 million units given 3 days apart (total dose 4.8 million units)	2.4 million* units (1.2 million units in each buttock)	1st, 3rd, 6th, and 12th months. Should revert to non- reactive (may require more than 12 months)
Latent (Early or late)	Spinal fluid non- reactive	As for Primary	As for Primary	As for Primary	<i>Early latent:</i> As for primary and secondary syphilis
	No spinal fluid examination	600,000 units daily (total dose 6 to 9 million units)	1.2 million units every 3 days (total dose 6 to 9 million units)	3.0 million units at 7 day intervals (total dose 6 to 9 million units)	<i>Late latent:</i> Every 6 months for 2 years. A static or falling titer does not require treat- ment
LATE (Asymptomatic and symp- tomatic neurosyphilis; cardiovascular and benign late syphilis)		600,000 units** daily (total dose 6 to 9 million units)	1.2 million units** every 3 days (total dose 6 to 9 million units)	3.0 million** units at 7 day intervals (total dose 6 to 9 mil- lion units)	<i>Neurosyphilis:</i> Serum and spinal fluid every 3 mo. for one year then every 6 mo. for 2nd year. Titer should remain static or decline slowly. Spinal fluid should show no cells within 6 mo. and have normal protein at one year. <i>Cardiovascular and Late Be- nign:</i> Every 6 mo for 2 years. A static or falling titer does not require treatment.
Syphilis in Pregnancy	First diagnosis	As above depending on stage	As above depending on stage	As above depending on stage	Monthly until delivery, then as for appropriate stage. Re- sponse as noted for appropri- ate stage
	Subsequent preg- nancy with no change in titer	No treatment	No treatment	No treatment	Monthly until delivery. Should remain static
Congenital	Under 2 years	100,000 units per Kg body weight in divided doses at 2 or 3 day intervals	100,000 units per Kg body weight in divided doses at 2 or 3 day intervals	50,000 units per Kg body weight in single dose	1st, 3rd, 6th, and 12th months should rapidly become non-reactive
	2 to 12 yrs. or weight less than 70 lbs. (spinal fluid non- reactive)	100,000 units per Kg body weight in di- vided doses at 2 or 3 day intervals	100,000 units per Kg body weight in divided doses at 2 or 3 day inter- vals	50,000 units per Kg body weight in single doses	1st, 3rd, 6th, and 12th month then every 6 months for second year. Titer may remain static or fall slowly
	More than 12 years or more than 70 lbs. (spinal fluid non- reactive)	As for Latent	As for Latent	As for Latent	6 month intervals for 2 years. Titer may remain static or fall slowly
	Spinal fluid reactive	As for Late	As for Late	As for Late	Serum and spinal fluid every 3 mo. for one year then every 6 mo. for 2nd year. Return of spinal fluid cell count and protein to normal indicates cure. Serum and spinal fluid may have static or very slowly falling titer

*Los Angeles County Public Health Department recommends a second dose of benzathine penicillin G at one week for a total dose of 4.8 million units.

**Los Angeles County Public Health Department recommends 9 million units as a minimum total dose.

women with either congenital or acquired syphilis who were normal until adulthood but then began to have rapidly progressive sensori-neural hearing loss and vertigo. Only two had attacks of interstitial keratitis. These cases will be briefly summarized.

Case 1: Five years ago a 29-year-old Negro woman telephone operator noted progressive deafness and tinnitus on the right. Hearing loss fluctuated over the next two years with eventual involvement of the left ear. Infrequent attacks of vertigo were noted. Four years earlier she had a typical attack of interstitial keratitis of the right eye. There have been no other neurological symptoms. A serologic test at age 15 was positive, and she was treated with penicillin at that time.

Physical examination revealed a 70 to 90 decibel hearing loss in both ears, with poor discrimination. The VDRL was reactive in 1:2 dilution, the FTA-ABS test was positive, the CSF VDRL was non-reactive and the colloidal gold curve was flat. Extensive metabolic tests were normal. After prednisone 60 mg four times a day and ten daily doses of penicillin, 600,000 units intramuscularly, her hearing improved to a 40 decibel loss on the right and 60 decibels on the left with a 20 percent increase in speech discrimination. She has remained improved for the past six months without a maintenance dose of steroids.

Case 2: The patient, a 34-year-old white woman, was born to parents who both had syphilis at the time of her birth. She had typical Hutchinson's teeth and in her late teens had intermittent painful swelling of the knees and episodes of interstitial keratitis. In the past six years she has had progressive hearing loss, tinnitus and vertigo, with bilateral involvement. She was re-treated three times with penicillin but on examination three years ago had an average hearing loss of 40 decibels on the right and 60 on the left with 32 percent speech discrimination on the left and 100 percent on the right. Hearing fluctuated dramatically, with often severe drops on the left. Vertigo was frequent and re-treatment with 20 million units of intravenous penicillin and probenecid a day was given for 30 days. She felt symptomatically slightly improved for three to four months but then had another sudden 20-decibel sensori-neural decrease in hearing on the right. Prednisone was added and there was then a dramatic decrease in vertigo, an increase in speech discrimi-

nation and decrease in tinnitus. Backache, intermittent knee pain and constant photophobia also diminished. Ampicillin, 6.0 gm, plus probenecid, 2.0 gm per day were given for 20 days without additional improvement. Each time prednisone was discontinued, severe recurrence of symptoms followed. The patient's hearing does not fluctuate while she is taking 5 mg of prednisone a day.

Case 3: Ten years ago the patient, a 54-year-old woman, had a typical attack of "Ménière's syndrome" with explosive severe left-sided deafness, tinnitus and vertigo, then gradual improvement in hearing. She remained well until one year ago when recurrence of the same symptoms was noted during a period of intense emotional stress. She had primary syphilis 30 years earlier, for which she received heavy metal treatment, then penicillin therapy in 1962 and 1963.

On physical examination she was found to have almost no hearing on the left, and audiometry confirmed the severe sensori-neural loss with no speech discrimination. A 20 to 30 decibel sensori-neural loss was also present on the right. Caloric testing revealed diminished responses to 30° C and 44° C irrigation on the left. The VDRL was reactive in 1:1 dilution, Reiter's test was negative, and the FTA-ABS test was positive. Initially vertigo and tinnitus worsened and constant unsteadiness occurred. A brief course of steroid treatment brought no significant change. A six-week course of ampicillin and probenecid was begun which initially was associated with a feeling of fullness in the head, but during the past three months she has had a decided improvement in equilibrium and a slight decrease in tinnitus and she has been able to drive for the first time in a year.

Case 4: Four years ago the patient, a 50-year-old white woman, noted sudden total deafness on the left associated with tinnitus and vertigo. A diagnosis of internal auditory artery occlusion was made. In the past three years she has had slowly progressive fluctuating hearing loss on the right plus constant disequilibrium and mild vertigo. Physical examination confirmed near total deafness on the left, and a 20 to 30 decibel loss on the right. The only other significant finding was that the right pupil was slightly less reactive to light than the left and reacted slightly better to accommodation than to light. One serum VDRL was negative with a negative Reiter test and TPI, but reactive FTA-ABS. The CSF showed reactivity of the Kolmer test on one occasion but non-reac-

tivity on another, with a flat colloidal gold curve. Lupus erythematosus (LE) preparations and numerous anti-nuclear antibody tests were negative. The patient was treated for five weeks with ampicillin and probenecid, but still showed some fluctuation of hearing. Addition of steroids in initially high doses followed by a maintenance dose of 5 mg of prednisone has been associated with no progression of hearing loss during the past two years. Unsteadiness and vertigo have been rare during that period.

Case 5: The patient, a Negro woman 55 years old, has had episodic vertigo for seven years and a slowly progressive mild loss of hearing. Physical examination four years ago revealed a 30 decibel flat hearing loss bilaterally. Caloric testing showed slightly less response on the right than on the left. She was considered to have bilateral Ménière's syndrome. Numerous VDRL tests were normal. She remained symptomatic for the next three years. Extensive x-ray studies including pneumoencephalography were normal. Repeat serology a year ago revealed a negative VDRL, positive FTA-ABS test and reactive TPI test. Hearing loss had progressed to 40 decibels bilaterally. The patient finally recalled a possibly luetic lesion on her face some 40 years earlier that had been treated with mercury. On receipt of the positive reports on FTA and TPI tests, she was treated with ampicillin and probenecid for five weeks and prednisone for one week. On audiometry two months later, the recording was the best in four years, with a 10 decibel speech reception threshold bilaterally. Her condition has remained stable with very little vertigo and no additional hearing loss.

Case 6: A 31-year-old Negro woman was treated with vasodilators for over four years because of "bilateral Ménière's syndrome" with a 10 to 15 decibel hearing loss, fluctuating vertigo and tinnitus. Several VDRL tests have been negative but recent TPI and FTA-ABS tests were reactive. Treatment with ampicillin and probenecid is under way.

In summary, three of these patients had been previously treated and re-treated with the conventional drug regimen for syphilis of up to 12 million units of penicillin and still showed late progressive inner ear or eighth nerve dysfunction. I also have seen a progressive case of general paresis, five to

six patients with progressive tabes dorsalis and three young patients who had syphilis in the past with cerebral stroke-like patterns or spinal artery occlusive syndromes, all occurring after treatment and in the absence of cells and increased protein in the CSF. It is alleged that these late manifestations are due to some "auto-immune" reaction, but recent findings that have demonstrated treponemal organisms in over 12 organs in previously treated patients should raise the possibility that active infection still exists. No other neurotropic bacterial infection of the nervous system is associated with such severe late progressive tissue destruction except the late fibrotic effects of tuberculous or other bacterial meningitides where intense adhesive arachnoiditis with hydrocephalus can explain most of the symptoms.

The reports from Smith and others of recovery of viable treponemes from the eye and other organs in previously treated cases like ours have been of great interest.⁴⁻⁸ Many of these patients showed serologic abnormalities only on the FTA-ABS test.^{4,5} Live organisms were aspirated from the anterior chamber of the eye; they were motile, resembled *T. pallidum* under the darkfield microscope and stained with a fluorescein-tagged antibody against *T. pallidum*. Subsequently, treponemes have been recovered from the spinal fluid, lymph nodes, liver, brain, synovial fluid, temporal artery, aorta, pharynx, foot ulcers and other organs in previously treated cases. Some of these cases had been re-treated with extremely high doses of penicillin—up to 500 million units in some instances.

Patients that have shown evidence of the most rapid tissue destruction in my own small experience are those with inner ear involvement as reported above. Such patients may classically present in early adulthood with "bilateral Ménière's disease" with slowly progressive bilateral sensorineural hearing loss with a rather flat curve on audiometry. However, some patients may have explosive symptoms somewhat suggestive of internal auditory artery occlusion. Eventual progression to bilateral total deafness is the rule and vestibular symptoms may be severe. Such symptoms persist despite repeated, conventional doses of penicillin. It is possible that most cases of bilateral Ménière's disease should be considered to be due to congenital syphilis until proven otherwise. Certainly three of our patients who were VDRL-negative, TPI-negative but FTA-positive, and clinically suspect because of other signs or a his-

tory of primary infection, are illustrative of this difficult diagnostic problem. It is extremely important to recognize such patients because recent evidence suggests that steroid therapy may halt the progression of inner ear damage.⁹ Hahn et al¹⁰ found a favorable response to cortisone therapy in some cases of deafness due to congenital syphilis and Patterson¹¹ reported similar findings. Our own small experience is also suggestive that long-term low dosage steroid therapy may halt the progression of the inner ear destructive process. It is too early to know whether intensive retreatment with oral ampicillin and probenecid alone has stabilized the condition of some of these patients. However, these experiences with inner ear syphilis challenge the notion that a late autoimmune or vascular degenerative reaction is the sole reason for the symptoms. The possibility that active infection is responsible has gained further support from the report of Mack et al that treponemes were demonstrated in the temporal bone in a previously treated syphilitic patient.¹²

Although the dramatic ocular and inner ear syndromes are certainly provocative enough to raise the question of persistent treponemal infection, there are large numbers of other patients who have shown progressive nervous system damage after conventional penicillin treatment. Our own small experience with progressive tabes, spinal vascular syndromes and certain hemispheric degenerative syndromes is too meager to draw conclusions, but a recent series from the National Institutes of Health demonstrated that 31 of 100 patients with general paresis who had been adequately treated ten years earlier had new, gross neurologic deficits on reexamination, such as major hemiplegia, amyotrophy, ocular motor paralysis, increased dementia or other signs.¹³ In that report it was postulated that there were three potential explanations for the occurrence of these new neurologic signs after treatment with penicillin: (1) that the dosage of penicillin may have been inadequate, (2) that the effect of penicillin on the spirochete may have been transient, and (3) that the tissue of the brain may have been permanently damaged before treatment, making the patient more susceptible to other central system disease. This latter possibility has been raised in some of our cases where probable meningo-vascular involvement predisposed to earlier cere-

bral infarction from superimposed atherosclerosis in the distribution of the same vessels.

The body of evidence to date suggests that these progressive nervous system destructive changes are due to the presence of live organisms and that the current treatment of neurosyphilis is often inadequate. The treatment failures are probably explained by inadequate concentration of penicillin in certain tissues unless the cases can be explained by development of organisms resistant to penicillin. This seems unlikely with the reports of clearing of the anterior chamber of the eye of treponemes when adequate doses are given. The most impressive series on this point is from Goldman at the Massachusetts Eye and Ear Institute where 40 patients with various ocular findings suggestive of congenital syphilis showed live motile treponemes which stained with fluorescein-tagged antitreponemal antibodies.⁷ These patients were treated with large doses of intravenous penicillin, but many had persistent treponemes on reaspiration of the anterior chamber. Only after a two to six-week regimen of ampicillin, 6 gm a day, and probenecid, 2 gm a day was there clearing of the anterior chambers.

The above experiences with the late progressive complications of neurosyphilis and the continuing lack of similar manifestations with other bacterial neurotropic infections has led me to use the high oral dosage regimen. If a patient has a "bilateral Ménière's syndrome," with or without other manifestations suggestive of syphilis, and if the FTA-ABS test is positive, a presumptive diagnosis of syphilis is made and intensive retreatment begun. High doses of corticosteroids (40 to 60 mg of prednisone a day) for one to four weeks, followed by maintenance therapy of 5 mg a day, are employed if no response to antibiotics alone is noted or if the initial otologic symptoms suggest acute occlusion of the internal auditory artery. Although there is a possibility of false positive FTA-ABS tests, this probably represents less than 1 or 2 percent of the total positives.¹

Changes in the FTA-ABS titer after intensive retreatment with the above ampicillin-probenecid regimen have not yet been reported, although the clinical response has been beneficial in certain cases, particularly those in which there was ocular inflammation. We must reserve further judgment about making a drastic alteration of the conventional proposals for treatment of syphilis, but the brunt of the responsibility now must be borne by

those who can convincingly show that these patients with progressive destructive changes, in whom motile organisms similar to *T. pallidum* have been identified, do *not* have drug-resistant or inadequately treated active infection.

Modern-Day Serologic Diagnosis of Syphilis

James N. Miller, Ph.D.:^{*} The difficulty which confronts the physician in his attempt to diagnose syphilis becomes apparent when one considers not only the diverse early and late clinical manifestations of the disease, but also the problem of latency which can occur either through the spontaneous healing of the early lesions or through their failure to develop. The physician must rely heavily upon serologic evidence when confronted with a patient exhibiting (1) no definite history of either exposure or the disease, (2) no specific treponemal therapy, and (3) absence of clinical findings or the presence of diverse manifestations which may or may not be referable to syphilis.

Non-Treponemal Tests

The term *non-treponemal* is often used synonymously (and erroneously) with "serologic tests for syphilis" (STS). These tests employ as antigen an active phospholipid obtained from normal mammalian tissue (referred to as *cardiolipin*) and fortified with both lecithin and cholesterol; they measure the presence of an antibody in the serum termed *reagin* (reagin should not be confused with the same term used to describe skin-sensitizing antibody in patients with human atopic allergies).

Venereal Disease

Research Laboratory (VDRL) Slide Flocculation Test

The VDRL slide flocculation procedure is used most frequently in the United States and is recommended as a screening procedure by the National Center for Disease Control, Venereal Disease Branch. It has been well standardized and is described in detail in the Manual of Tests for Syphilis, 1969.²⁰ In untreated syphilis, VDRL antibody begins to appear in the blood one to three weeks after the appearance of the primary lesion and continues to rise during the course of the early

disease, approaching 100 percent during the secondary stages. As the disease progresses toward latency and late disease, reactivity tends to diminish, dropping to 75 percent during the late latent and tertiary stages. Any degree of VDRL reactivity in the serum of a patient should *always* be followed by a quantitative determination, despite the fact that further testing may be necessary to establish a treponemal etiology. Most patients with primary syphilis show conversion to non-reactivity within six to twelve months after adequate penicillin therapy. Occasionally, the titer will either decrease to persist at low levels, or remain at the same level as before treatment, the latter situation being referred to as "Wassermann-fast"; in neither instance is this an indication for re-treatment. Only if the reagin titer increases by at least two tube-dilutions should re-treatment be instituted. If treatment is begun during the secondary stages, it may take as long as 18 months before VDRL antibody disappears. As with primary syphilis, complete disappearance may or may not occur, additional therapy being required only when significant titer increases are observed. Adequate treatment during latency or late syphilis usually has very little effect upon the titer of reactive patients; complete serological reversal to non-reactivity is rare. Again, additional therapy is indicated only when the titer increases.

The VDRL slide test designed specifically for use on spinal fluids²⁰ should be routinely employed with cell count and total protein determinations in the investigation of asymptomatic and symptomatic neurosyphilis. Although false positive VDRL tests *rarely* occur, some laboratories have experienced variability in sensitivity with the cardiolipin Kolmer test and therefore prefer to use either the VDRL and Kolmer together or the latter alone. The diagnosis of neurosyphilis is established by the reactivity of the non-treponemal tests, while the cerebrospinal fluid cell count and total protein correlate with disease activity to some degree. Without serologic reactivity on spinal fluid, increases in cell count and total protein could be indicative of other neurological disorders. Decreases in the cell count and subsequent return to normal are the best indication of successful therapy in patients with neurosyphilis. The usual persistence of elevated total protein and spinal fluid reagin for years following adequate treatment preclude their use as reliable criteria.

The diagnosis of congenital syphilis in newborn

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infants born of mothers with a history of either definite or questionable or no treatment for syphilis can be fraught with considerable difficulty in the absence of obvious clinical manifestations. This stems from the fact that reagin crosses the placental barrier, thereby making it impossible to determine whether cord-blood reactivity is due to passive antibody transfer or active infection. A definitive decision, based on serological evidence, may take as long as three to four months during which time passively transferred antibody disappears or active infection manifests itself as a persistence of, or increase in, titer. Therefore, diagnosis by thorough physical examination must be relied upon in evaluating the need of a newborn infant for treatment.

"Rapid" Tests on Unheated Plasma or Serum

A series of non-treponemal tests has been developed since 1957 which use unheated plasma or serum and a VDRL antigen which contains choline chloride to inactivate interfering heat-labile substances and a chelating agent for stability. Procedures such as the rapid plasma reagin (RPR) card test^{15,16} were designed largely for the rapid screening of large population groups where difficulty occurs in locating patients for treatment; however, they have had limited use. A large number of hospital and blood banking facilities are using a modification known as the Plasma Crit test¹⁷ (PCT) to screen blood donors and infants. In addition to the rapidity with which the test can be performed, the fact that it can be utilized on plasma from hematocrit determinations makes it convenient. The test, however, shows greater reactivity than the VDRL, thereby necessitating the repeat testing of all reactive sera by the latter procedure.

The use of RPR card test antigen (containing charcoal particles for macroscopic visualization of the flocculation reactions) in an automated reagin test (ART) has given results shown to compare favorably with the VDRL slide test.^{18,19} It utilizes modified Technicon Auto Analyzer equipment and is capable of sampling at the rate of 100 sera per hour. The ART should prove useful as a screening procedure for those laboratories with large numbers of sera to test daily, as well as for those laboratories with automated equipment for blood grouping.

Treponemal Tests

Treponemal tests in diagnostic use today are those procedures which employ as antigens either (1) virulent *T. pallidum* in the living or killed state or (2) a protein extract from the antigenically-related, cultivatable, *Treponema reiteri*. The need for such immunologically specific procedures became evident shortly after the development of the first non-treponemal test by Wasserman in 1906, at which time it was suspected that diseases or conditions other than syphilis could elicit positive reactions. However, the diverse clinical course of syphilis made it impossible to distinguish, with any degree of certainty, the false positive (FP) reaction from that due to syphilis. Further, the absence of reagin from the blood of some patients with late syphilis made an accurate differential diagnosis extremely difficult.

Treponema Pallidum Immobilization (TPI) Test

The obvious necessity for treponemal procedures led to the development of the TPI test in 1949.²⁰ The test is based upon the principle that actively motile, virulent, *T. pallidum* are rendered non-motile or "immobilized" in the presence of syphilitic serum and guinea pig complement under suitable environmental conditions. In the presence of non-syphilitic serum and complement, the organisms remain actively motile under the same environmental conditions. Although simple in theory, the test is technically complex and therefore limited in its use to a relatively few specialized laboratories. The complexities stem mostly from the fact that the virulent, Nichols strain of *T. pallidum* employed as antigen must be maintained by intratesticular passage in rabbits. Further, the sensitivity of *T. pallidum* to physical, chemical, and environmental factors makes it difficult to maintain actively motile antigen suspensions for the necessary incubation period.

The TPI test measures the presence of a specific "immobilizing" antibody in the serum of patients with syphilis. The antibody begins to develop late in the primary or early in the secondary stage, at a time when reagin has already appeared. In contrast to reagin, which gradually declines as the disease progresses to latency and late syphilis, immobilizing antibody continues to increase during the secondary stages, remaining at relatively

high levels throughout the course of the untreated disease.

Inasmuch as immobilizing antibody remains for years after adequate treatment initiated beyond the early stages of the disease, a reactive TPI test indicates present or past syphilitic infection and cannot be used as an index of cure.

The excellent specificity of the TPI test and thus its ability to differentiate FP reactions from those due to infection with *T. pallidum* has been confirmed by numerous investigators. Data accumulated in our laboratory, as well as in many other treponemal research laboratories, have shown that approximately 50 percent of patients with reactive or weakly reactive non-treponemal tests, in the absence of a history or epidemiological evidence of syphilis, are FP reactors on the basis of non-reactive TPI results. In our experience any acute or chronic disease and many other conditions can elicit an FP reaction of either the acute or chronic variety. Of particular interest is our finding of FP reactivity among pregnant women,¹⁹ narcotic addicts²⁰ and blood donors (unpublished data). It has also been well established that an FP reaction can make its appearance months or even years before the actual onset of chronic diseases, particularly collagen vascular disorders. Thus, it becomes quite evident that patients with no definite evidence relating to syphilis, but exhibiting a reactive or weakly reactive STS, must be subjected to specific treponemal testing; the presence or absence of syphilis in these situations cannot otherwise be ascertained. It should be apparent that the use of blood for transfusions from donors with FP reactions is as contraindicated as is the use of such blood from those patients in whom a diagnosis of syphilis has been established.

The TPI test has not only enabled us to aid the physician in his attempt to differentiate syphilis from other disease processes and conditions, but has also allowed us to gain considerable insight into the mechanism of host-spirochete interaction.

The search for a specific treponemal test, simpler and more economical to perform than the TPI test and therefore utilizable in clinical and public health laboratories, led to the development of two procedures which are at present employed by such laboratories for diagnostic purposes. They are the Reiter protein complement-fixation (RPCF) test, which is known also as the Kolmer Reiter protein (KRP) test, and the fluorescent treponemal antibody-absorption (FTA-ABS) test.

Reiter Protein Complement-Fixation (RPCF) or Kolmer Reiter Protein (KRP) Test

The RPCF (known also as the KRP) test was developed in 1953.²¹ It is a complement fixation test utilizing as antigen a protein extracted from virulent *T. reuteri* which is related to an antigen of virulent *T. pallidum*. The RPCF test measures an antibody distinct from reagin and immobilizing antibody. Although RPCF antibody parallels reagin by appearing early in the course of syphilitic infection, it exhibits a sensitivity of only 80 percent during latent and late syphilis in comparison to the TPI test. Some investigators have questioned the specificity of the RPCF test; however, in my experience the specificity compares favorably with that of the TPI test. The variable effect of treatment upon RPCF antibody precludes its use either as a criterion for cure or as a determinant of the status of disease.

Fluorescent Treponemal Antibody-Absorption (FTA-ABS) Test

The FTA-ABS test is a modification of the fluorescent treponemal antibody test developed in 1957²² and employs killed, virulent *T. pallidum* as antigen. Both tests are based upon the principle that specific antibody in the serum of patients with syphilis binds to the *T. pallidum* antigen and, because of its globulin nature, combines with fluorescein-labeled anti-human globulin. The resulting *T. pallidum*-antibody globulin fluorescein-labeled anti-human globulin complex results in the fluorescence of the spirochete. In the absence of antibody, treponemal fluorescence should not occur. In the original FTA procedure, approximately 25 percent false positive reactions were obtained on normal sera, presumably due to the presence of circulating antibody formed in response to the common antigens of non-pathogenic treponemes normally found in the mouth and genitalia. The FTA-ABS test attempts to solve the problem by utilizing a heat-stable extract of non-pathogenic *T. reuteri* as a "sorbent" which bind non-specific common treponemal antibody and leaves only specific antibody, if present, to combine with *T. pallidum*. Although the FTA-ABS antibody appears earlier in the course of the disease than does TPI antibody, they tend to closely parallel one another in sensitivity during latent and late syphilis. Treatment beyond the early stages

has no predictable effect upon FTA-ABS reactivity and therefore cannot be used either as a criterion for cure or to determine the status of the disease.

Although the specificity of the test is considered by many to be comparable to that of the TPI test, the available evidence necessitates some qualification in this regard. In 5 to 30 percent of the "problem sera" tested in clinical laboratories, a low level of fluorescence is obtained which cannot be considered as either reactive or non-reactive and is therefore reported as "borderline." At present the clinical significance of these reactions is unknown and represents a "gray area" in our attempt to differentiate syphilis from FP reactions. While it is conceivable that such reactions are due to low levels of non-specific antibody, common to *T. pallidum* and absent from *T. reuteri*, the possibility also exists that such reactions represent specific antibody against virulent *T. pallidum*.

The technical performance of the FTA-ABS procedure is not simple. Training in the principles and use of the fluorescence microscope, as well as in the technical aspects and protocol of the test, is essential before instituting its routine use.

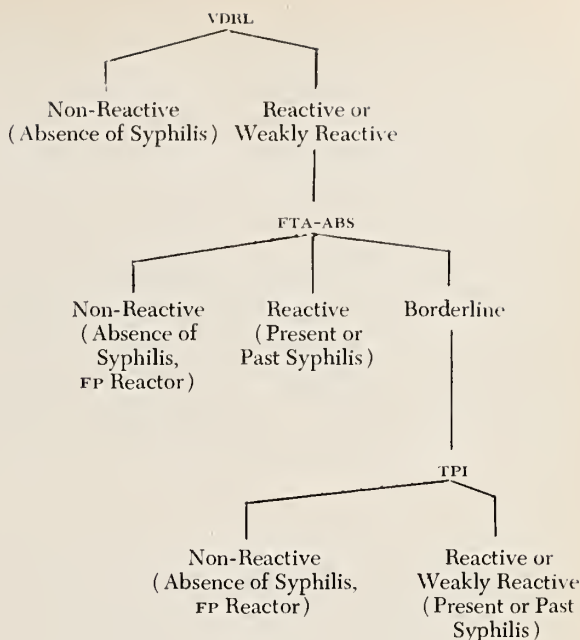
Testing of Diagnostic Problem Cases

The diagnostic problem case is usually detected by the use of a non-treponemal test employed as a screening procedure in pre-marital, pre-natal, and physical examinations, hospital admissions, and special mass testing programs; the VDRL slide flocculation test is recommended in the United States. Patients with a reactive or weakly reactive test and exhibiting a questionable or no definitive history of syphilis, with or without clinical manifestations, can be further tested by one of the following recommended plans.

FTA-ABS—TPI PLAN

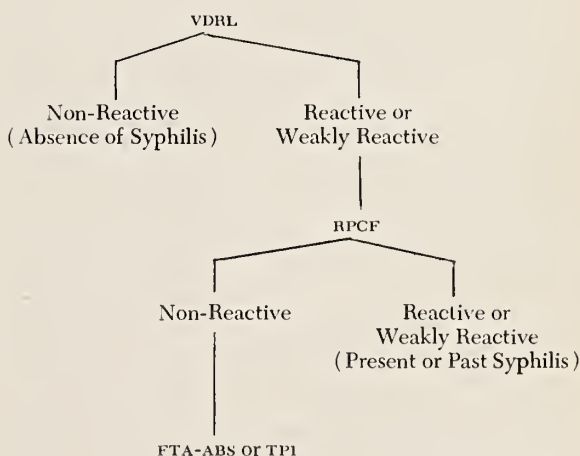
Perform the FTA-ABS test. If *reactive*, the diagnosis of present or past syphilis is established. If *non-reactive*, syphilis is considered to be absent, and the patient is classified as an FP reactor. If the test is *borderline*, no conclusion can be drawn, and the TPI test should be carried out. If the TPI test is *reactive* or *weakly reactive*, the diagnosis of present or past syphilis can be made. If *non-reactive*, syphilis is considered to be absent and the patient is classified as a FP reactor.

The plan may be schematically diagrammed as follows:



RPCF—FTA-ABS—TPI PLAN

Perform the RPCF test. If *reactive* or *weakly reactive*, the diagnosis of present or past syphilis is established. If *non-reactive*, an FTA-ABS or TPI test should be carried out with the interpretation of results as described under the FTA-ABS—TPI plan above. The TPI test should be carried out in all instances where the FTA-ABS result is *borderline*. Interpretation of TPI results is as previously described. The plan may be schematically diagrammed as follows:



Interpretation of Results as
Described for the FTA-ABS—TPI PLAN

Patients with a non-reactive VDRL in whom very early or late syphilis is suspected should be subjected to one of the specific treponemal test plans outlined above, inasmuch as non-reactivity with the non-treponemal tests can and does occur during these stages of the disease.

It must be borne in mind that any of the described treponemal and non-treponemal tests can exhibit reactivity in patients with other treponemal diseases such as yaws, pinta, and endemic syphilis. While these diseases do not occur in the United States, they must be considered as part of the differential diagnosis if the patient has resided or traveled in areas where they are prevalent.

The Future

A passive hemagglutination test for syphilis (TPHA) developed in 1966²³ holds great promise as a useful tool in the serodiagnosis of syphilis. It is a specific treponemal test based upon the principle that formalinized, tanned sheep red cells coated with an ultrasonic lysate of virulent *T. pallidum*, agglutinate in the presence of specific syphilitic antibody. Preliminary evaluation of the test as a manual procedure and as a semi-automated microhemagglutination procedure indicates a high degree of sensitivity and specificity.^{24,25} If extensive field studies prove satisfactory, it is conceivable that this procedure could serve as a valuable adjunct to those treponemal tests presently employed in routine and specialized diagnostic laboratories.

Concluding Remarks

Dr. Turner: The information provided by the discussants should be valuable in the approach to evaluating patients with suspected or confirmed syphilis. Even if the physician increases his awareness and skill in the detection and treatment of syphilis, the public health problem will not be solved. Conscientious reporting of cases of syphilis by private physicians, coupled with epidemiologic techniques and education of the public, is necessary for successful control of the disease. This "cure and case finding" approach may contain the epidemic and reduce the incidence of infectious syphilis, but true eradication will await the development of an effective vaccine. We are

fortunate that investigators such as Dr. Miller persevered during the lean years, when the promise of penicillin made research in syphilis seem almost unnecessary. We know now, as Dr. Nelson has pointed out, that certain aspects of the pathophysiology and treatment of syphilis remain unsettled, and the difficult problem of vaccine development has yet to be solved. We shall be looking to the research laboratories and to the clinical investigators for the answers to these problems.

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MEDICAL STAFF CONFERENCE

Anemia and Heart Failure

Association with Cardiomyopathy and Multiple Blood Transfusions

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* The association of anemia and heart failure always poses the very difficult therapeutic problem of whether blood transfusions will improve or worsen the heart failure. A patient in which this decision had to be made will be discussed today. The case will be presented by Dr. Stewart Spies.

DR. SPIES:† A 66-year-old Caucasian woman was admitted to Moffitt Hospital in January 1971 for evaluation of dyspnea during physical effort. She had been well until eight years ago when megaloblastic anemia was diagnosed. Vitamin B₁₂ and folic acid therapy did not correct the anemia, and hemolysis and aplastic bone marrow developed. These complications required frequent and multiple blood transfusions. Several months before the patient was admitted to Moffitt Hospital a paroxysmal supraventricular arrhythmia developed and digitalis therapy was instituted. On physical examination the patient was observed to be chronically ill and icteric, with sinus tachycardia, cardiomegaly, a loud precordial systolic murmur, mild heart failure, increased pigmentation of the skin, and hepa-

tosplenomegaly. Laboratory studies revealed anemia (hemoglobin 3.8 grams per 100 ml, hematocrit 14 ml per 100 ml) and a high serum level of iron (272 µg per 100 ml), chemical diabetes (fasting blood glucose 168 mg per 100 ml), and jaundice (total bilirubin 5.1 mg per 100 ml). Urinalysis yielded hemosiderin, but no blood was found in the stool. An electrocardiogram showed sinus tachycardia with occasional atrial premature beats and left ventricular hypertrophy. An x-ray film of the chest showed cardiomegaly with prominent pulmonary veins and other abnormalities compatible with congestive heart failure. Transfusion of four units of washed red blood cells was carried out and the hematocrit rose to 23 ml per 100 ml. The patient improved symptomatically and at present is free of breathlessness during physical effort.

DR. SMITH: We are fortunate to have Dr. Celia Oakley to discuss this case today.

DR. OAKLEY:* This patient had severe chronic anemia, congestive heart failure, and tissue hemosiderosis resulting from intravascular hemolysis and multiple blood transfusions. We shall discuss

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†Stewart Spies, M.D., Intern in Medicine.

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the etiologic features of her congestive heart failure and the adverse effects of anemia and transfusion hemochromatosis on cardiac performance.

In patients with chronic anemia, the red blood cell volume is decreased, the plasma volume is increased, and the total blood volume is usually within normal limits or low. The cardiac output is elevated, and there is a fall in peripheral vascular and peripheral vasodilatation.¹ The vasodilatation is independent of the sympathoadrenal axis and telologically it is assumed to result because the diminished oxygen-carrying power of the blood is not completely compensated by the increased blood delivery to tissues.² However, the real mechanism is unknown. The arteriovenous oxygen difference is narrow in patients with anemia, which indicates that the increased cardiac output is greater than it should be if the extraction of oxygen by tissue were complete. The increased output results from increased heart rate and stroke volume. These hemodynamic changes are also responsible for the murmurs that are so often heard in patients with chronic anemia.³ These "flow-murmurs" arise in the outflow and inflow tracts of the right or left ventricles and manifest as precordial mid-systolic ejection or mid-diastolic murmurs, respectively. A third heart sound is also commonly heard. Cardiac dilatation seen on the x-ray film may result from the increased cardiac output and stroke volume or from heart failure. Experimental work has shown that cardiac output rises at hemoglobin levels between 4 and 9 grams per 100 ml but rarely at higher levels. When the hemoglobin falls below 4 grams per 100 ml, heart failure is common. Thus, in uncomplicated chronic anemia, heart failure is infrequently seen unless the hemoglobin value is below 4 grams per 100 ml.⁴

As evidenced by the wide arteriovenous oxygen difference between coronary arterial and coronary sinus venous blood, the oxygen extraction by the myocardium is almost complete. When the oxygen capacity is reduced in patients with anemia, myocardial hypoxia inevitably develops. Thus, in patients with severe chronic anemia the myocardium, particularly the subendocardial region of the left ventricle, is hypoxic, cardiac performance is impaired, and microscopic degenerative changes develop. Histologically, the myocardium, particularly the subendocardial surface, shows infiltration of fat. In older patients who have coronary artery disease, heart failure occurs at hemo-

TABLE 1.—*Cardiomyopathies Seen at the Royal Postgraduate Medical School, London, over a Ten-Year Period Ending December, 1970*

Patients Presenting as Cardiomyopathy			
248			
Hypertrophic		Congestive	
120		128	
Familial	Sporadic	Primary	Secondary
39	81	104	24

globin levels higher than 4 grams per 100 ml, and angina is common. The anginal syndrome may also occur in patients free of ischemic heart disease when severely profound anemia develops.⁵

In addition to the anemia, there was also the likelihood that the patient presented today may have had cardiomyopathy. Cardiomyopathy denotes a deficit in heart performance that is not a result of a valvular, congenital, hypertensive, or atherosclerotic disorder. Arrhythmias, including heart block, and cardiac failure are often the first manifestations of cardiomyopathy. Cardiomyopathy may be primary, if the process affects only the heart, or secondary, if the disease also affects other organs—for example, hemochromatosis. However, the underlying pathological process of cardiomyopathy is often ill defined, and such an idiopathic case is also termed primary cardiomyopathy. Naturally, semantic confusion arises when various series are then compared. At the Royal Postgraduate Medical School, London, we find a functional classification less confusing and clinically more useful (Table 1).⁶ Hypertrophic cardiomyopathy is diagnosed when left ventricular hypertrophy is present, but left ventricular dilatation and heart failure are absent. Obstruction to left ventricular outflow is common at some stage in the disorder, with signs and symptoms similar to aortic valve stenosis. However, the treatment of idiopathic hypertrophic subaortic stenosis is medical, not surgical.

In familial hypertrophic cardiomyopathy, there appears to be a dominant inheritance with variable penetrance in the affected families. Familial hypertrophic cardiomyopathy does not differ clinically or hemodynamically from its noninherited

sporadic counterpart. Congestive cardiomyopathy accounts for the remainder of the primary and secondary cases and is diagnosed when heart failure is present. A specific cause of the heart failure is found in only a minority of patients. When associated disease is found in other organs, secondary cardiomyopathy is diagnosed; all secondary forms are also congestive.

Hemodynamically, in congestive cardiomyopathy the cardiac output and ejection fraction is low and the residual volume and ventricular filling pressures are elevated. Clinically, breathlessness, edema, and a dilated or "baggy" left ventricle are present. Etiologically, congestive cardiomyopathy is infective, toxic, metabolic, endocrine, collagen-vascular, neurological, hematological, degenerative, or senile in origin.

When no cause is found, a previous viral infection is the most probable. However, it is curious that chronic myocardial failure develops so infrequently in patients with proved acute viral myocarditis. In the few cases in which acute viral myocarditis does "progress" into chronic myocardial failure, all signs of the viral infection disappear. Alcoholic cardiomyopathy is also common, but it may be that alcohol exacerbates and triggers a previous myocardial abnormality rather than effects chronic myocardial failure per se. Prepartum cardiomyopathy is common in parts of the world where poverty and low standards of living are rife and specific nutritional deficiencies or toxins have not yet been identified.

Blood disorders account for a small proportion of secondary types of cardiomyopathy. Polycythemia and microangiopathic hemolytic anemia are associated with vascular occlusions, the former with venous thrombosis and coronary arterial occlusions and the latter with obstruction by split fibrin products in the small arteries in the heart, brain and kidney. Amyloid deposition associated with multiple myeloma is also a cause of myocardial infiltration and congestive heart failure. In patients with hemochromatosis, the tissue iron stores are increased and heart failure may occur. Deepening of skin color, diabetes, hepatosplenomegaly, and jaundice may all be present; bronze diabetes is an apt synonym for the entity. An elevated level of iron in the serum and hemosiderin in the urine strongly suggest the diagnosis, but a definite diagnosis can only be made when tissue damage is documented by histological examination of a biopsied liver specimen. Recently, how-

TABLE 2.—*Classification of Hemochromatosis**

- I. Idiopathic—develops in absence of known causes of iron overload; often family history of iron storage disease
 - A. Prefibrotic stage; increased stores and absorption with a positive family history
 - B. Fibrotic stage—organ damage
- II. Secondary—(more common than idiopathic)
 - A. Chronic hemolytic anemias
 - B. Repeated blood transfusions for aplastic anemia
 - C. Alcohol ingestion with excess dietary iron (Bantu hemochromatosis)
 - D. Congenital defects in iron metabolism leading to iron loading; for example, transferrin deficiency, thalassemia major, and pyridoxin-responsive anemia

*Tissue damage with increased total body iron stores (assessed by tissue biopsy and response to repeated venesection or chelating agents).

ever, a characteristic urine iron response to deferoxamine methanesulfonate (Desferal®) has been described⁷ as confirmatory, obviating the liver biopsy.

Congestive heart failure or arrhythmia develops in 30 percent of patients with hemochromatosis. Increased iron stores and fibrosis involving the myocardium are likely responsible for the congested state, but heart failure may also be related to an impairment of enzyme systems, especially those of the glycolytic cycle, a block in xanthine oxidase production or an impairment of myoglobin synthesis.^{8,9,10,11} In patients with idiopathic hemochromatosis anemia is not present, but parenchymal stores of iron are increased and when accompanied by fibrosis are pathogenic for congestive heart failure due to hemochromatosis.^{12,13}

In hemosiderosis, the reticuloendothelial stores of iron are increased and fibrosis and heart failure are not present.¹⁴ Hemolytic anemia and repeated transfusion of blood give rise to secondary hemochromatosis or secondary hemosiderosis (Table 2).¹⁵ When heart failure develops in a patient who requires frequent multiple blood transfusions for chronic refractory anemia and when the hematocrit is 25 per cent or greater, a working diagnosis of transfusion hemochromatosis is legitimate.¹⁶ Sickle cell anemia is a classic exception to this rule and heart failure often occurs in the absence of hemochromatosis.¹⁷ Interestingly, heart murmurs in these patients are often incorrectly diagnosed as evidence of rheumatic heart disease. Treatment of hemochromatosis is re-

peated venous phlebotomy. The objective of therapy is to decrease tissue iron stores, which hopefully prevents continuation of tissue fibrosis. Since phlebotomy is impractical in patients with refractory anemia, iron-chelating agents are used; however, to date, this approach has been disappointing.

The patient presented here has cardiac infiltration with iron, but she is not considered to have cardiac hemochromatosis. Heart failure developed only when the hemoglobin level was less than 4 grams per 100 ml, that is, when she became severely anemic. Furthermore, the congestion developed years after diagnosis and treatment of megaloblastic anemia by repeated blood transfusions and was easily reversed by elevation of the level of hemoglobin. Heart failure, therefore, was induced by the severe anemia. However, the increasing amounts of iron in her heart may lead to eventual cardiac fibrosis and transfusion-effected heart failure, although the time course of this process cannot be forecast. To date, it is not possible to establish a correlation between the duration and severity of hemolytic anemia and the number of blood transfusions required for ultimate development of the myocardial incapacity.

TRADE AND GENERIC NAMES OF DRUGS

Desferal® deferoxamine methanesulfonate

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SURGICAL TREATMENT OF OPEN-ANGLE GLAUCOMA

What are your criteria for surgery in chronic open-angle glaucoma?

"I use the classic criteria. If visual field loss is progressing, despite the best tolerable medical therapy, surgical therapy is indicated.

"Let me make just a point about this field loss progression. I think it is extremely important to emphasize that visual field testing must be done with the pupils at least fairly well open because false field defects and some which simulate classic glaucomatous defects surprisingly well can be produced by miosis alone and particularly by miosis if there is early or incipient cataract present. So don't hesitate to dilate the pupils to test the visual fields in these people. In our hands, the drug Mydriacyl® has been the best thing for counteracting even the strong miotics, the strong anticholinesterase drugs that we've had before. It will open the pupils quite quickly even in the face of these drugs. Of course, it doesn't keep them open very long, so it's an excellent drug to use.

"If with the open pupils we get field loss with an isopter comparable to the 2 to 1,000 or a comparable isopter on the Goldman perimeter (which we increasingly like to use for our final judgments), we will go ahead with filtering surgery in the chronic open-angle glaucoma."

—Panel Discussion, The Need for Therapy in Glaucoma
Extracted from *Audio-Digest Ophthalmology*, Vol. 7, No. 23, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057

Important Advances in Clinical Medicine

Epitomes of Progress -- Radiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Radiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Radiology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Radiology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

Role of Laparotomy in Staging of Hodgkin's Disease

Laparotomy has been used with increasing frequency in the initial evaluation of patients with Hodgkin's disease. This procedure consists of a splenectomy, wedge biopsy of the liver, para-aortic lymph node biopsy (of nodes that appear suspicious on the lymphangiogram), and an open bone marrow biopsy. In young females who may have the pelvis irradiated, the ovaries are moved

to the midline (oophoropexy) in order to enable their shielding during pelvic irradiation. Staging laparotomy of this kind was done on 100 consecutive untreated and unselected patients with Hodgkin's disease.

Liver involvement is uncommon and has not been observed in the absence of involvement of the spleen.

Enlargement of the spleen is a poor criterion for involvement, as half of these patients with clinically enlarged spleens did not have disease in this organ. Unsuspected disease in the spleen was detected in approximately one-fourth of the patients. Seven patients had disease in the splenic hilar lymph nodes, occasionally occurring as the only site of disease below the diaphragm.

The staging laparotomy is an extremely useful technique to accurately stage Hodgkin's disease

below the diaphragm because involvement may remain occult with routine diagnostic procedures previously employed.

RONALD W. THOMPSON, M.D.

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Disseminated Multiple Pulmonary Calcifications Due to Coccidioidomycosis

Localized single (or a few) pulmonary calcifications following primary coccidioidomycosis occurs in up to 10 percent of the patients examined. However, multiple pulmonary calcifications following primary coccidioidomycosis have rarely been encountered. Two cases of multiple primary foci of pulmonary coccidioidomycosis simulating metastasis, showing progressive calcifications on serial roentgenograms were encountered. One patient was followed for 12 years and another for four years. The progress of calcifications within the multiple lesions from their inception to the end stages was studied and the calcifications did not become apparent until approximately two years after the initial infection. In one case there was progression of calcifications for ten years before they became static. The most common cause for disseminated small calcifications throughout the pulmonary parenchyma is histoplasmosis. Numerous disseminated small calcifications occurring following primary coccidioidomycosis is a rare exception rather than the rule.

E. NICHOLAS SARGENT, M.D.

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Pitfalls in Post-Herniorrhaphy Diagnosis of Gastric Lesions

With the older and simpler types of operation for esophagogastric hiatus hernia repair such as application of the hiatus or gastropexy, there was little cause for error in the interpretation of the postoperative stomach. Nevertheless, at least one case was reported where the patient went to surgery again with a greater curvature lesion stimulating a tumor, probably at the site of chronic pressure upon the area of the hiatus before herniorrhaphy.

Following the more sophisticated procedures of fundal plication of the Belsey and Nissen type, in which the fundus is actually sutured to envelop the esophagus, there is a greater potential for error with the production of deformities of the fundus which may simulate a neoplasm. Several cases have been observed in the postoperative period when this erroneous conclusion could have been drawn if the operative findings and procedure had not been known.

It is suggested that a gastrointestinal series in the recent postoperative period be done on all patients who have undergone hiatus herniorrhaphy, particularly the fundal plication types, to avoid future confusion of changes with that of a gastric neoplasm.

EDWARD R. DANA, M.D.

REFERENCE

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Multiple Pulmonary Fibroleiomyomatous Hamartomas

Multiple pulmonary fibroleiomyomatous hamartomas of the lung are extremely rare and only eight cases have been reported. These cases are

of interest not only because of their infrequent occurrence, but also because they are an exception to the rule that benign tumors of the lung are nearly always solitary lesions. All patients are relatively asymptomatic women, between 38 and 58 years of age. The roentgenographic findings consist of multiple, well-circumscribed, non-calcified, rounded nodules in both lungs. These benign tumors which have been shown to slowly increase in size on serial roentgenograms can only be differentiated from metastatic malignant neoplasms by surgical resection of one of the nodules and histopathologic study.

E. NICHOLAS SARGENT, M.D.

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"honeycomb" appearance (see film). The method described is virtually diagnostic and without serious hazard.

E. R. GREENBAUM, M.D.

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Hystero-graphy in the Detection Of Hydatidiform Mole

In the earlier periods of gestation, from approximately 12 to 14 weeks, the clinician is often faced with a diagnostic problem in the differential diagnosis of hydatidiform mole from incomplete or threatened abortion.

Often at this stage of gestation, the patient presents with vaginal bleeding but has not passed molar tissue and, on physical examination, the uterus may not be unduly enlarged.

High urinary gonadotropin levels at this stage of gestation may be seen in normal pregnancy.

The absence of roentgenographic visualization of a normal fetal skeleton is again within the range of normal at this early stage.

We feel that the best radiographic approach in making this differential diagnosis is by use of transabdominal hystero-graphy. The hystero-graph will show the multiple grape-like structures which constitutes the mole as multiple filling defects, which lends an over-all "moth-eaten" or

Superior Marginal Rib Defects

Although the diagnostic implications of inferior marginal rib defects or notching have been well documented, the occurrence of superior marginal rib defects or erosions has not received the attention it deserves. Superior marginal rib defects, which are related to abnormal bone remodeling resulting from an imbalance between osteoblastic and osteoclastic activity, have been demonstrated in a variety of conditions. Disturbances of osteoblastic activity (decreased bone formation) resulting in superior marginal rib erosions or defects, have been encountered in paralytic poliomyelitis, amyotonia congenita, collagen diseases, localized pressure for various reasons, osteogenesis imperfecta, Marfan's syndrome, and radiation damage. Disturbances of osteoclastic activity (increased bone resorption) in hyper-

parathyroidism, hypervitaminosis D and acromegaly have also resulted in bone erosions with superior marginal rib defects. A few cases have been encountered which are idiopathic and not due to any demonstrable associated disease.

Although the findings are not specific for any one cause, they are encountered with sufficient frequency that the recognition of this sign on a chest roentgenogram should lead one to direct a further generalized investigation of the patient to arrive at a more definitive diagnosis.

E. NICHOLAS SARGENT, M.D.

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Food-Barium Meal of Value in Diagnosing Gastric Outlet Obstruction

Radiologists have been accustomed to diagnosing obstruction to the outlet of the stomach by retention of liquid barium within it for a period of three to six hours. When the stomach was emptied of barium before this time period the referring doctor was apprised that the patient had no evidence of obstruction. Over a period of years it became apparent that barium did not really represent the usual stomach content, and consequently efforts were made to monitor the emptying of ordinary food from the patient's stomach.

Methods have been devised by different observers in which steak, hamburger, or a breakfast of choice are given to the patient followed by a glass of barium, which mixes with the food, and x-ray films are obtained a few hours later. Through examinations on normal patients the time at which the stomach would be expected to empty of a food-barium mixture has been determined.

With these methods some patients with normal upper gastrointestinal series have been found to have obstructing lesions of the gastric outlet, and

patients with lesions of the outlet showing no evidence of obstruction with regular barium studies have been found to have obstruction. It seems likely that in the symptomatic patient without evidence of obstruction by regular barium studies, some type of food-barium evaluation for retention should be done.

EDWARD R. DANA, M.D.

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Raskin HF: The application of the barium burger motility study in clinical significant gastroduodenal obstruction not recognized by conventional roentgenologic studies. *Gastroenterology* 58:986, 1970

Percutaneous Needle Biopsy of Pulmonary Lesions for Cell Culture

Percutaneous needle biopsy of pulmonary lesions under fluoroscopic control is a safe means of obtaining tissue for pathological evaluation. A Vim-Silverman needle is introduced into the lung lesion and the core sample is removed. The procedure may be done on an outpatient basis with relatively little preparation.

The core sample obtained is aspirated into a sterile isotonic solution and transferred into McCoy's medium. With cell growth, chemosensitivity studies can be performed.

JAMES D. COLLINS, M.D.

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Treatment of Retinoblastoma

The management of patients with retinoblastoma based on the experience of treatment of 54 patients with this disease at the UCLA Center for Health Sciences reveals that the chances for survival are excellent, even in patients who have disease involving both eyes when treated by surgical operation or surgical operation and radiation therapy.

When the disease is of limited extent, the results are excellent when the patients are treated by radiation therapy and there is a very good chance of preserving vision.

The treatment of patients with retinoblastoma requires coordinated teamwork between the pediatrician, ophthalmologist, anesthetist, and radiation therapist.

The use of ketamine (Ketalar®, Parke, Davis) anesthesia permits rapid induction of the anesthesia without respiratory or circulatory depression. Endotracheal intubation is not necessary. The patients awaken in a short time. They can be treated as outpatients.

RONALD W. THOMPSON, M.D.,
RICHARD C. SMALL, M.D., AND
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Bagshaw MA, Kaplan HS. Supervoltage linear accelerator radiation therapy—VIII. Retinoblastoma. *Radiology* 86:242-246, 1966

Emergency Treatment of Pneumothorax

Symptomatic pneumothorax, whether small, large, or under tension, and a pneumothorax in any patient with underlying pulmonary disease or previously diagnosed poor pulmonary reserve, can be afforded immediate treatment by a simple technique of insertion of a newly designed pneu-

mothorax catheter. Particularly, in emergency treatment of pneumothorax complicating needle aspiration biopsies the system can be used to prevent any serious complications. The chest tube is made of a thin-walled Teflon No. 9 (French) radiopaque material. The tubing is 14 inches long and the distal 3 inches have multiple perforations to allow an easy flow of air into the tube lumen. A No. 18 cannula, 8 inches long containing an obturator is inserted through the most proximal side hole in the tube rendering the distal part of the catheter inflexible. The cannula fits tightly against the inner wall of the distal end of the catheter and prevents leakage of air. After making a small stab wound in the skin, usually at the level of the second anterior interspace, in the mid-clavicular line, the catheter is inserted by pushing the cannula and catheter simultaneously into the pleural space. The stiffening cannula is then removed, the catheter is inserted further into the pleural space, and the proximal end is attached to a one-way Heimlich drainage valve. The method is simple and safe, and does not require any advance surgical skill or training. The use of this procedure is suggested as a reliable expedient for immediate treatment of any pneumothorax that may present as an emergency in the radiology department.

E. NICHOLAS SARGENT, M.D.

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Heimlich HJ: Valve drainage of pleural cavity. *Dis Chest* 53:282-287, Mar 1968

Angiographic Demonstration of Renal Vein Invasion in Renal Carcinoma

Angiographic demonstration of renal carcinoma with associated collateral veins about the kidney has a high association with renal vein invasion by tumor. The presence of these veins on abdominal aortograms and selective renal angiogram is referred to as the "collateral vein" sign.

The basis of this sign is the rich anastomotic network of veins draining the kidney. The collateral veins include the subcapsular, capsular

(located in perinephric fat), ureteric, adrenolumbar, paravertebral, hemiazygous, gonadal, lumbar and inferior phrenic veins.

The high association of this finding with tumor invasion is a valuable preoperative sign that should alert the radiologist and urologist not only to the presence of renal vein invasion but also to the size and number of vessels that may be encountered at operation.

JACK I. EISENMAN, M.D.

REFERENCE

Eisenman JI, Finck EJ, O'Loughlin BJ: Collateral vein sign: Angiographic demonstration of renal vein invasion in renal carcinoma. *Radiology* 92: 1256-1261, May 1969

New Techniques in Pulmonary Angiography

In spite of recent advances in pulmonary scanning, pulmonary angiography is still an important and, indeed, the most reliable diagnostic test for delineating pulmonary thromboembolism. New techniques have been devised to both facilitate and improve the quality of the study.

A percutaneous right femoral vein approach allows rapid catheterization reliably permitting use of catheters of a more suitable size than may be possible through the more conventional approach by venous cutdown on the antecubital fossa. A small reverse curve to the distal tip combined with a pigtail facilitates the procedure even further as well as enhancing its safety.

Another technique worthy of note is segmental pulmonary arteriography which has its greatest value in chronic recurrent pulmonary embolism. Segments of the lungs are selectively catheterized and injected with contrast medium using very fine detail technique allowing demonstration of old residual of embolic disease.

J. H. GROLLMAN, JR., M.D.

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Ranniger K: Pulmonary arteriography: A simple method for demonstration of clinically significant pulmonary emboli. *Am J Roentgenol Radium Ther Nucl Med* 106:558-562, Jul 1969

Transfemoral Selective Coronary Arteriography

Selective coronary arteriography may be accomplished safely by way of a percutaneous transfemoral approach utilizing specially designed preformed catheters. These catheters are designed to seek out the coronary ostia without the necessity of the extensive manipulations required in the more established Sones technique which involves a flexible catheter passed by way of the brachial artery. Because of the somewhat greater selectivity permitted by the various femoral techniques, improved detail of filming can be obtained which is so important for proper patient selection for the recently developed saphenous vein aorto-coronary bypass procedures.

J. H. GROLLMAN, JR., M.D.

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Selective Arterial Infusions of Vasoconstricting Agents in the Control of Gastrointestinal Hemorrhage

A recent outgrowth of the use of angiography in the diagnosis of gastrointestinal bleeding has been the selective intra-arterial infusion of vasoconstricting drugs to control acute gastrointestinal hemorrhage.

Both pitressin and a combination of epinephrine and propranolol have been used to control arterial hemorrhage, while pitressin has been used to reduce portal venous pressure and thus control variceal bleeding. After the site of bleeding has been demonstrated angiographically, the

vasoconstricting drug is infused selectively into the artery supplying the bleeding point. Repeat angiograms in addition to clinical findings may be used to determine whether the bleeding has ceased. Pitressin has been infused into the superior mesenteric artery for as long as two weeks in the control of variceal hemorrhage.

The results have so far been extremely encouraging and it is hoped that many patients may be spared emergency operation.

ROBERT K. GRAY, M.D.

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Nusbaum M, Baum S, Kuroda K, et al: Control of portal hypertension by selective mesenteric arterial drug infusion. *Arch Surg* 97:1005-1013, Dec 1968

Radionuclide Detection of Left-to-Right Cardiac Shunts

Large numbers of children, and occasionally adults, present a diagnostic problem of functional murmur versus congenital heart disease. Often, cardiac catheterization is necessary to make a correct diagnosis. Recently a simple radioisotopic technique has been perfected which enables detection of left-to-right shunts.

The procedure involves an intravenous injection of technetium-99m pertechnetate while imaging with an Anger scintillation camera over the heart and lungs and simultaneously recording the study on magnetic tape. A radionuclide cardiac angiogram is obtained, from which a pulmonary vascular dilution curve of the appearance and disappearance of isotope in the lung can be extracted. The pulmonary vascular dilution curve is analyzed in a specific manner which clearly differentiates the normal curve from one which reflects left-to-right shunting of blood through the lungs. Correlation with cardiac catheterization data has shown this test to be very sensitive to the presence of even very small left-to-right shunts.

This test is being used as a screening procedure for children with heart murmurs of unde-

termined significance. It appears to be a safe, highly reliable and valuable clinical tool in the evaluation of the pediatric cardiovascular patient.

NAOMI P. ALAZRAKI, M.D.

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Radionuclide Studies as a Guide to Status of the Renal Transplant

There are two basic radioisotopic imaging studies that can be performed to follow the function of the transplanted kidney. They are the radionuclide renal angiogram and the radiohippuran renogram. These tests are also widely used in evaluation of renal function and renal artery stenosis in the general population.

The radionuclide angiogram is performed by intravenous injection of a bolus of technetium-99m pertechnetate and imaging with the scintillation camera over the transplanted kidney. Normally the distal abdominal aorta, the iliac vessels and prompt accumulation of the tracer material in the transplanted kidney are observed, indicating patency of the vascular supply to the transplanted kidney.

The renogram is performed by imaging with the scintillation camera, or a probe placed over the transplanted kidney to record the appearance and excretion of I_{131} labeled hippuran which is injected intravenously. The hippuran is excreted by the renal tubules and, providing there is patent vascular supply to the kidney and no obstruction of urine flow, the appearance and disappearance of tracer in the kidney reflect renal tubular function.

Transplant rejection and acute tubular necrosis both give abnormal results and are often indistinguishable by the hippuran renogram alone. However, the radionuclide angiogram usually continues to indicate adequate renal perfusion in the case of acute tubular necrosis but de-

creased perfusion in rejection. The combination of the two studies will in many cases distinguish rejection phenomena from other processes.

NAOMI P. ALAZRAKI, M.D.

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Radionuclide Spleen Scans

In the evaluation of a patient with splenomegaly or trauma to the left upper quadrant, the radioisotope scan of the spleen may be used as a valuable screening test. Splenic scans may be helpful in detecting infarcts, hematomas, abscesses, cysts, hemangiomas and metastases. The scan can be used to follow the resolution of splenic infarcts or hematomas and the progress of a patient with splenic abscesses under treatment.

Today the most widely used radioisotopic method of visualizing the spleen involves use of Technetium-99m sulfur colloid, the same agent used for liver scanning, injected intravenously. The colloidal material is phagocytized by the reticuloendothelial cells of the body, which are abundant in the liver and spleen. Another agent, Chromium-51 tagged to denatured red blood cells, is occasionally used when uptake by the liver is undesirable, since this agent will be sequestered almost exclusively by the spleen. This can be helpful in looking for accessory splenic tissue.

In cases where physical examination of the left upper quadrant leaves doubt about the status of the spleen, splenic size and morphology can be quite accurately evaluated by obtaining multiple views of the spleen after intravenous injection of the appropriate radionuclide.

NAOMI P. ALAZRAKI, M.D.

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Ultrasonic Cardiovascular Diagnosis

In addition to the more familiar use of diagnostic ultrasound in the detection of pericardial effusion and mitral stenosis, newer applications have considerably broadened the scope of echocardiography.

It is now possible to diagnose other lesions affecting the mitral valve, such as idiopathic hypertrophic subaortic stenosis and prolapsing mitral valve, by recognizing characteristic displacements of the anterior leaflet during systolic. The introduction of indocyanine green as an ultrasonic "contrast" material has allowed identification of many intracardiac echoes, including those of the aortic root. Distinct echoes arising from the aortic cusps can now be routinely visualized and an estimate made of their thickness.

In many reports, proper transducer placement has allowed accurate and reproducible measurement of the left atrial diameter, as well as indicating the presence of tumor or thrombi in that chamber. Similarly, the left ventricular diameter can frequently be recorded in both systole and diastole, allowing computation of stroke volume.

It is anticipated that more widespread use of this technique will produce still further diagnostic applications.

GEORGE R. LEOPOLD, M.D.

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Abdominal Echography

Ultrasonic tomography is playing an increasingly greater role in the diagnosis of a wide variety of abdominal disorders. In addition to determining alterations in the contour of the

abdominal organs, it is also possible to assess the consistency of masses if proper attention is paid to gain settings of the instrument.

The liver, gallbladder, pancreas, spleen, kidneys, and aorta have all been demonstrated in both normal and pathological states. Since the technique is totally non-invasive, it may be repeated serially, thereby providing information concerning the natural course of many disorders that have previously required more complicated radiologic procedures of greater risk.

The two-dimensional representation of anatomy also provides excellent positional information for biopsy or puncture of visualized abnormalities (for example, renal tumors and cysts). This positional information is likewise important in the placement of radiotherapy ports and subsequent reduction in port sizes as the tumor regresses.

GEORGE R. LEOPOLD, M.D.

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Bone Scanning in the Pre-treatment and Follow-up of Malignant Disease

Radionuclide bone scanning appears to constitute the most sensitive method of evaluating early metastasis to bone. In numerous series, including almost every common type of primary tumor, the bone scan was of great value in demonstrating early metastasis in a surprising number of cases in which neither bone pain nor x-ray evidence for metastasis was present. Strontium-85 has been generally replaced by short half-lived isotopes Strontium-87m and Fluorine-18 as the radionuclide of choice for bone scans.

Bone scans are used in many centers as a routine preoperative screening test in cases of carcinoma of the breast. Demonstration of an otherwise unrecognized metastasis may alter the surgeon's choice of operation.

In addition to tumor, other abnormalities of bone, including osteomyelitis, fracture, periosteal reaction, and many other benign and malignant

conditions can cause localized tracer uptake on the bone scan. Correlation with x-ray will usually exclude these other conditions as the cause of abnormality on the scan.

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Radiation Dosage and the "Rad Equivalent Therapy"

To many, the roentgen, the unit of given dose in air, and the rad, the absorbed dose, have always been somewhat confusing. At first glance, therefore, the introduction of another unit, in this case the concept of the RET (rad equivalent therapy), would only seem to add to the confusion. However, with treatments given over varying periods of time, a unit to combine the daily dose, the number of fractions and the total time was desirable.

A correlation of these factors had been represented graphically by Strandqvist, and for the skin by a time-dose formula by von Essen, but the recently published formulated "slide-rule" introducing the RET, as a "nominal standard dose" unit (Winston et al) has been fairly rapidly accepted. It is usual to calculate one's standard RET dose for a particular tumor based in a normal treatment regime, and from this an alternative fractionation pattern is simply calculated. Although yet to be fully proven both in theory and practice, it does enable one to vary the treatment regime within certain limits to suit the patient, while at the same time brings the dose up to a level that each radiotherapist considers to be curative and yet within tissue tolerance.

DAVID G. SEAY, M.B., F.F.R.

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Angiography of Pediatric Abdominal Masses

Abdominal aortography and selective visceral arteriography may provide a valuable adjunct in the evaluation of pediatric abdominal masses. The procedure is performed by any experienced angiographer by percutaneous Seldinger puncture of the common femoral artery. The morbidity of pediatric arteriography is chiefly caused by arterial thrombosis (incidence usually about 4 percent) at the puncture site.

Arteriography of primary liver tumors (hepatoblastoma or infantile hemangioendothelioma) pro-

vides indispensable information to the pediatric surgeon in planning hepatic lobectomy. Arteriography delineates the frequent hepatic vascular anomalies and the extent of tumor.

Arteriography of pediatric retroperitoneal tumors (Wilms' tumor or neuroblastoma) should be reserved for enigmatic cases. The extent, recurrence, or response of tumor to therapy are delineated. When bilateral Wilms' tumor is suspected, arteriography confirms or excludes the presence of a contralateral tumor.

ROBERT E. CLARK, M.D.

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New Knowledge About HGH

THE PAST DECADE has witnessed an explosion of new knowledge concerning the structure, secretion and function of human growth hormone (HGH). During this short time, HGH was purified and shown to be effective in the treatment of hypopituitary dwarfism; a specific HGH immunoassay was developed, leading to a rapid increase in our knowledge concerning the regulation of growth hormone secretion and providing a specific test for the diagnosis of growth hormone deficiency and hypersecretion; the primary amino acid sequence of the HGH molecule was determined, and within the past year this complex peptide hormone was synthesized.

Elsewhere in this issue, VanderLaan has reviewed the control of growth hormone secretion in man. It is apparent that the regulation of growth hormone secretion and the mechanisms of HGH action are quite complex. As with the other pituitary hormones, the secretion of HGH appears to be regulated by a specific hypothalamic releasing factor or hormone (GRF or GRH).¹ Although the purification of GRF and determination of its structure have not yet been accomplished, it is likely that GRF will prove to be a short peptide molecule, similar to thyrotropin releasing factor (TRF) and melanocyte stimulating hormone inhibiting factor (MIF).² The numerous stimuli for HGH secretion, both chemical and neuronal, appear to act on the hypothalamus, releasing GRF into the hypothalamic-hypophyseal portal veins, which then stimulates HGH release from the pituitary gland. The physiological regulation of HGH secretion, however, has still not been completely unraveled. VanderLaan has reviewed the various pharmacological and stressful stimuli of HGH secretion, as

well as the recent experiments which have demonstrated a spontaneous peak in plasma HGH concentrations following the onset of sleep. Recent evidence also suggests that growth hormone can regulate its own secretion by means of an auto-feedback system. The plasma HGH response to both insulin-induced hypoglycemia and arginine infusion are markedly attenuated following increases in the plasma concentration of HGH (for example, following exercise) or following exogenous HGH administration.^{3,4} Complete understanding of the normal daily regulation of HGH secretion however, will require the development of techniques which can monitor HGH secretion rates over long periods of normal activity; a promising method has recently been described by Kowarski et al.⁵

The mechanisms of action of HGH on the peripheral tissues are also quite complex. Aside from its obvious role in the stimulation of growth and protein synthesis, HGH appears to play an important part in the daily regulation of fat and carbohydrate metabolism.⁶ HGH is an important stimulus of lipolysis, elevating plasma free fatty acid concentrations; it directly augments the pancreatic secretion of insulin and antagonizes the peripheral effects of insulin on glucose uptake. Most of these metabolic effects appear to be secondary to the direct action of HGH on RNA and protein synthesis. The effects of HGH on cartilage metabolism and bone growth, however, appear to be indirect, involving the participation of a secondary hormonal mediator.⁷ Salmon and Daughaday⁸ demonstrated that serum from normal individuals contains a hormonal substance which stimulates sulfate uptake in cartilage; they named this material "sulfation factor" (SF). Sulfation factor is deficient in the serum of hypopituitary persons, but can be induced within 24 to 48 hours by treating them with HGH. Addition of HGH to hypopituitary serum *in vitro*, however, does not induce sulfation factor activity. Furthermore, hypophysectomized rat cartilage removes sulfation factor activity from serum *in vitro*, but has little HGH-

binding activity.⁷ Thus HGH appears to induce the generation of sulfation factor (probably in the liver), which in turn stimulates cartilage anabolism and replication. Daughaday⁷ has suggested that the intermittent and irregular pattern of HGH secretion would be a poor system for the regulation of orderly cell growth; the sulfation factor system may have evolved to integrate the net effect of multiple HGH peaks, thus providing a modulated system for the regulation of bone growth.

Disorders of HGH secretion have long been recognized: acromegaly and gigantism resulting from excessive HGH secretion, and proportionate dwarfism from HGH deficiency. VanderLaan has reviewed the complexity of the hypothalamic and pituitary abnormalities in the etiology of acromegaly. It is now apparent that pituitary dwarfism is a heterogeneous group of disorders which result from disturbances in all parts of the hypothalamic-hypophyseal-target organ complex.⁹ A clinical syndrome of pituitary insufficiency might theoretically result from developmental or degenerative diseases of the hypothalamus, deficiency of hypothalamic releasing hormones, developmental or degenerative lesions of the pituitary, deficient secretion or structural abnormalities of the pituitary hormone molecule, or by target organ unresponsiveness to hormonal action. Examples of most of these mechanisms have been documented in the pathogenesis of pituitary dwarfism.⁹ Hypothalamic abnormalities associated with HGH deficiency have been described in association with the holoprosencephaly syndromes,¹⁰ anencephaly¹¹ and septo-optic dysplasia.¹² HGH deficiency secondary to degenerative hypothalamic destruction has been described in histiocytosis X.¹³ Congenital absence of the pituitary¹⁴ and degenerative lesions of the pituitary (for example, hemochromatosis¹⁵) have been found to result in HGH deficiency. Target organ unresponsiveness to the actions of HGH appears to be the cause of the African pygmies' short stature;¹⁶ whereas in Laron type of dwarfs the basic defect appears to involve either an inability to generate sulfation factor, or a structural mutation in the HGH molecule.¹⁷

Among the idiopathic forms of pituitary dwarfism, several mechanisms are likely, including a deficiency or structural defect in either GRF or the HGH molecule itself. Costom, Grumbach and Kaplan¹⁸ recently demonstrated that the primary defect in many panhypopituitary dwarfs lies in the

hypothalamus rather than the pituitary. They found that eight of nine hypopituitary dwarfs tested had a normal TSH response to exogenously administered TRF, indicating that the primary cause of their hypothyroidism was a deficiency of TRF. It is thus likely that their HGH deficiency is also due to deficient GRF secretion. The major implication of this important observation is that GRF may provide a practical substitute for HGH in the treatment of many patients with pituitary dwarfism. GRF appears to be a small peptide and should be more applicable to commercial synthesis than the large HGH molecule. Patients with isolated growth hormone deficiency could have a deficiency or structural abnormality of either GRF or HGH. The recessive inheritance of this disease suggests that it is probably secondary to a structural mutation which produces an altered functionally inert peptide hormone. Purification and synthesis of GRF should provide a sensitive test to determine whether the primary defect lies in the hypothalamus or pituitary in these patients. In those forms of pituitary dwarfism associated with a primary hypothalamic lesion GRF administration may well turn out to be the treatment of choice. Purified or synthetic preparations of HGH, however, will still be required for the treatment of those forms of pituitary dwarfism associated with a primary pituitary defect or a structural abnormality in the HGH molecule.

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United or Separate?

THE REAL ISSUE IN THE POLL of the membership which is to be begun September 1 is whether organized medicine in California will remain united or will separate, with many individuals and groups going different ways. There are those who will contend that this is not the case and that all that is at stake is one more expression of opinion in support of voluntarism as against compulsion, this time over the question of whether a physician exercises enough free choice when he joins or does not join his county medical association, knowing that in doing so he also joins the California Medical Association and the American Medical Association, or whether this free choice should now be extended to give him the further option of joining or not joining the CMA and AMA. The question to be posed to the membership—"Do you favor or oppose retaining the present system of unified membership in your county society, CMA and AMA?"—addresses itself to the real question.

These are times of revolutionary change. We have only to look around us to sense the enormity of what is occurring. Many, if not most, of what are generally thought of as the stabilizing elements of a social system are being seriously eroded, if they are not actually crumbling. This is apparent in the law and courts, in the educational system, in respect for the military and the police, and in the authority of the churches, to

cite a few pieces of the evidence. It is no longer possible to oppose or prevent this revolution. We are engulfed in it. Its hallmark so far has been fragmentation of the old order with little to propose for the new. The problems to be resolved are human problems and the needs to be met are human needs. Health and well-being are among the goals which are being sought. Medicine should take part in developing some of the new solutions. The question to be decided is how can medicine best play its role—united, or separate and fragmented?

Do not the issues of "voluntary" and "compulsory" seem somehow beside the point in the face of social revolution and cultural fragmentation? Everyone knows how physicians feel about free choice and compulsion. It has been voted on many times and in many ways. And it is a matter of record that both CMA and AMA have worked for voluntarism and against compulsion for as long as anyone can remember, and quite successfully too. Is this not a time to close ranks and not to scatter, to be united and not to separate? We should all favor retaining the present system of unified membership in county society, CMA and AMA.

Dealing in Futures

Part II—In Democratic Societies

A PREVIOUS EDITORIAL expressed the view that California and the country as a whole were investing in medical research and education as though only for today's market when actually they are dealing in futures—that is, spending money which has to be spent or invested today in order to buy or produce a product which can only be delivered at a later time when presumably it will be needed. The purpose of this editorial is to draw attention to a characteristic of democratic societies, be they institutions, organi-

This is Part II of an editorial to be published in three parts. Part I appeared in the July issue, and Part III will be published in the September issue.

zations or governments, which makes them peculiarly inept when it comes to dealing in futures.

It is a weakness of democratic societies that they have no good mechanism for consistent commitment in the dimension of time, especially time ahead. They seem to be almost completely devoid of any real capacity to recognize what quite evidently lies ahead, or to take the actions which must be taken now to adapt or prepare themselves for it. The fact is that democratically controlled societies are by nature oriented toward the present, to the solving of present problems and the preservation of present accomplishments. This seems to be primarily because the leaders and policy makers must always have an eye to winning the next election, and their constituents or voters are always much more concerned with what they perceive to be the realities of the present than what did happen in the past or might happen in the future. It is probably for reasons such as these that the problems of the future tend to get short shrift in democratic societies unless they are problems of the present as well.

This system worked well enough until fairly recently when it seems to be proving somehow inadequate. Perhaps the reason is that some of the most important problems are getting too complex and have too many roots in the past and too many implications for the future to be handled, or even understood and let alone solved, in the time interval between elections or annual meetings or whatever times leaders and policy makers must answer to their constituents in any democratic system. And, as if the existing complexities and unsolved problems of medicine and today's society were not enough, there is now a new and growing awareness that "nature bats last" (to quote a bumper sticker) when it comes to ecological survival, and quite evidently there will soon be new dimensions of futures when it comes to the control of population and pollution and the allocation and exploitation of resources. More sophisticated dealing in futures is rapidly becoming essential for democratic societies if either they or the human race is to survive or be healthy.

The present ineptness of democratic societies with respect to dealing in futures in the sense described must somehow be overcome. Democratic institutions, organizations and governments must develop a substantially greater capacity to think and plan beyond the crisis or emotion of the moment or the next election. They must develop

a clearer forward vision and a greater capability to do what must be done now to adapt and prepare themselves and the society they serve for what can be seen ahead. In short they must mature as instruments of planning, decision and action, and they must do this as rapidly as possible.

Venereal Disease Epidemic

GONORRHEA AND SYPHILIS are increasing alarmingly. The present epidemic, labelled "pandemic" by the American Social Health Association, began a little more than ten years ago. Venereal disease is principally an urban problem and most of the new cases are in young people, many of them in their teens. In Los Angeles, for example, an estimated 20 percent of the members of high school graduating classes have or have had either gonorrhea or syphilis. In the population of Los Angeles at large, the incidence of gonorrhea has trebled in less than 25 years; and as to syphilis, new cases (primary and secondary) rose 54 percent last year alone.

The epidemic has been brought about by a multiplicity of factors including increased sexual promiscuity, public apathy, failure to practice primary prevention, lack of successful casefinding on backtracking from infected patients, reduced education to the profession and public, and a complacency of the medical profession in the mistaken belief that venereal disease can be treated out of existence. Sexually active patients are not being instructed on how to avoid venereal disease and are not being periodically examined to see if they do become infected. Screening for venereal disease is not being carried out adequately in obstetrical and gynecological clinics, multipurpose clinics, on college campuses, among school dropouts, and at contraception clinics, although these are all likely places to discover cases and to set follow-up casefinding apparatus into motion.

Case management of individual patients is the responsibility of private physicians and public

health departments. Unfortunately it is not generally acceptable to the patient—hence to the physician—to have a case reported, although reporting is the first step toward the further casefinding which helps to halt spread of the disease. Further difficulties are that patients cannot always remember all sexual contacts and sometimes even those who are named cannot be found. Some carriers never come to medical attention and go untreated.

Treatment is a control measure only insofar as it reduces the communicability of infected patients. It will not result in disease reduction unless each infected patient's source and spread cases are also treated. This is not even a possibility unless physicians report each case they see to a public health department possessing trained personnel who can confidentially locate source and spread.

The ideal way to prevent a communicable disease is by immunization. There is no doubt that this would be the best way to control venereal disease; but a syphilis vaccine has yet to be produced, and since no active immunity is conferred by gonorrhea it is unlikely that there will ever be a vaccine for that disease.

Hence, while we can look forward to control of syphilis sooner or later, wide use of prophylaxis appears the only hope for reduction of gonorrhea. And only two groups, physicians and pharmacists, are in an ideal position to discuss prevention. Unfortunately many in both professions are not aware of all prophylactic procedures and products, and some are even reluctant to educate themselves in such matters or to pass this knowledge on to patients. Health departments often are wary of pressing vigorous campaigns to educate young people in prophylaxis, for they are subject to public pressures which can make them desist. The community itself must be first convinced before the health department can successfully operate a primary preventive program for venereal disease.

Prophylactic education involves building a sense of sound sexual values in young people. These values are not generally being instilled in youth by the family. In general, neither parents nor their children have accurate information or an inclination to discuss sexual activities; and public schools, because of scattered opposition to sex education, often are not willing to assist in engendering acceptable sex values in young people.

Among prophylactic measures that could be widely taught are such things as personal hygiene, douching, urination after contact, and the use of prophylactic kits and condoms. Persons who are opposed to the use of prophylactic devices can take antibiotics before sexual exposure. Many of these measures are quite as protective in homosexual as in heterosexual relations (about 50 percent of new cases of syphilis are transmitted by homosexual contact). An intravaginal agent (progonasyl), which has been marketed for more than forty years, is both contraceptive and prophylactic. Quite beyond these matters of instructions in prophylaxis, physicians themselves must adopt a procedure of prophylactically treating sex partners of infected patients.

Above all, we must recognize there is very little hope that either gonorrhea or syphilis can be diagnosed or treated out of existence. But much of it can be prevented, and an epidemic is urging an educational responsibility upon us.

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A Happy Choice

JOHN R. HOGNESS, M.D., is known only to a relatively few California physicians, but those fortunate enough to have made his acquaintance are certain that his appointment as the first full-time president of the new National Institute of Medicine is indeed a happy choice. It is much too early to predict what the influence or authority of this new Institute may turn out to be, but it is good to know that the physician who is to guide its formative years is a man of unusual common sense, and unusually broad interests, with an excellent track record as a medical school dean truly interested in medical practice, and as a high level administrator for health sciences and health affairs at the University of Washington. California physicians are sure to hear more of John Hogness and we predict that they will like what they hear. We wish him well.

The AMA Convention

A Report on Activities by the CMA Delegation

WHAT DOES THE American Medical Association House of Delegates really accomplish? What are the issues and how are they resolved? And just what results does the California Medical Association delegation to the AMA achieve?

Before reporting on the actions at the June 20-24 meeting of the AMA House of Delegates, let's look at the way the membership's interests become CMA-AMA policy.

For each 1,000 AMA-member physicians, CMA elects one delegate to the AMA House of Delegates, which meets twice a year. CMA now has 25 delegates, making up about 10 percent of the 246-member House. However, the strength and influence of the CMA delegation far exceeds its numerical proportion. It is said that "when the surf's up in California, the rest of the profession feels the waves."

It is noteworthy that 22 of the 98 resolutions considered by the AMA House were introduced by CMA's delegation and the batting average on them was high: eight CMA resolutions were adopted without change; four were adopted after minor amendment; four formed the basis of substitute resolutions; five were accepted for further study and disposition; and one was withdrawn because its intent was already being carried out. None of the 22 were rejected. Almost half the resolutions introduced by the CMA delegation were initiated by county medical society delegates at last March's session of CMA's own House of Delegates. This success rate demonstrates that the profession in California has a big say-so in AMA policies and actions. The CMA delegation also successfully promoted the candidacy of CMA Past-President Ralph C. Teall for the office of AMA vice president.

Anticipating success of this kind was an article in the June 18 issue of *Medical World News* which

was based on a questionnaire that had been sent to all the 246 AMA delegates. "The California delegation," the writer of the article reported, "boasts an astonishing number of leading speakers, according to the questionnaire respondents."

The story behind that statement is the hard work of the delegation elected to represent the profession in California. And here's how they do it.

After jointly discussing issues and resolutions with the CMA Council, CMA's 25 delegates, 25 alternate delegates, and officers go to the AMA convention. There the 50-plus physicians caucus for two hours over breakfast every morning, and delegation committees meet during lunch and dinner breaks. In between they cover reference committee hearings, push California resolutions, study reports and candidates for AMA office, consider every item of House business. And on the floor of the House, the delegation is articulate in pushing issues for action *now*, averting the delaying "refer, defer and table" route.

Here's a capsule report on accomplishments. Adopted as AMA policy were California resolutions:

- Stating that access to medical care is the right of every citizen, but that the citizen has the responsibility to seek it. The resolution also declared it the right of every physician to choose whom he will serve "and the conditions under which he will render this service."

- Calling for legislation "to remove legal and administrative obstacles to the distribution of birth control information, medication and devices by providers of medical care" and directing AMA to "conduct an effective scientific public education program on birth control information for family planning."

- Encouraging state and county medical soci-

eties to establish active liaison with their local school systems to provide educational lectures on health.

- Directing that an ad hoc committee develop opinion polls of AMA member attitudes on critical issues.

Other California resolutions that passed urged cooperation of medical societies with the American Hospital Association by providing information that would help in review of a hospital's application for AHA membership, when appropriate; federal hospital utilization review; assistance to diploma nursing schools; and expansion of medical emergency radio frequencies. Among California resolutions adopted after amendment were those concerning JCAH liaison with state associations, HMO study, SAMA's Medical Education and Community Orientation project, and cigarette advertising.

AMA's House also:

- Called for an all-out attack on drug abuse and venereal disease.

- Voted to continue its informational programs on national compulsory health insurance.

- Declared it in the public interest to preserve the physician's right to use and direct allied health workers.

- Received a report clearing the way for American-born foreign medical graduates to participate in approved U.S. internship programs without satisfying the foreign schools' internship and social service requirements.

- Adopted position-policy papers on "due process" in professional conduct review procedures; evaluation of the primary physician's assistant; perinatal intensive care; physician manpower and medical education; educational programs for med-

ical assistants; liaison with house staff; professional liability; AMA long-range planning and development; and teenage pregnancy.

- Heard AMA's new president, Dr. Wesley W. Hall, call for a constitutional convention "to streamline our governing process to suit the needs and pace of the 20th-century physician and the people." The delegates deferred action on this proposal until AMA's Clinical Convention next November.

At the House's opening session, your CMA's Audio-Digest Foundation was commended for contributing more than half a million dollars since 1956 for loans to medical students and for financial support to California's medical schools.

To sum up: the record of accomplishment of the CMA delegation clearly demonstrates the effective way in which California physicians' interests are represented in the AMA. The delegates and alternates from California in my estimation have clearly demonstrated their dedication to the best interests of their profession and their patients. At no time did they hesitate to act wisely and unselfishly for these interests. In so doing they have honored themselves, their state medical association and American medicine. I would like to take this opportunity to thank all members of our contingent—delegates and alternates—for this dedication and hard work.

It also seems evident that CMA's influence will be enhanced next year, when our delegation will surely be the largest at AMA, since the New York Medical Association will undoubtedly lose between five and ten delegates because of its membership drop.

SAMUEL R. SHERMAN, M.D.
Chairman, CMA Delegation to AMA

COOL PANTS OR EVEN NONE AT ALL

"I find a great many of my patients wearing the nylon and orlon panties with very tight panty girdles, and sometimes the pants will gather up in the middle of the introitus and create irritation to the labia minora and majora. I think that in patients who have any type of sebaceous cysts or vulvovaginitis the use of cotton panties is excellent. I particularly tell these patients that when they are at home and just doing their housework, it is best for them to go around without any pants at all to get as much aeration as possible."

—ABE MICKAL, M.D., New Orleans
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The Question:

SHALL ORGANIZED MEDICINE BE UNIFIED, or SEPARATE

Members of the California Medical Association are to be called upon in September to ballot on a question of great importance to the future of organized medicine: Shall membership in organized medicine—county medical society, California Medical Association, American Medical Association—be unified, or shall such membership be separate?

In the July issue we published statements pro and con which the Informed Membership Poll Committee had prepared from statements of position on both sides of the question that the committee had solicited from county societies and individuals.

Here, for the fuller information of our readers on this momentous question, we are presenting material representative of the arguments that the Committee digested in the statements printed in the July issue.

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No one, least of all doctors, likes the word "compulsory." If we must choose between "compulsory" and "voluntary," there are about two hundred years of American heritage that will stack the results heavily in favor of "voluntary."

Unfortunately, the choice is not that simple. The precedent has been established in California that if a doctor wishes to participate in organized medicine, he must support all levels of his organization, local, state, and national. Because of the large numbers of California doctors who belong to AMA, California has one of the larg-

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Though there are many lesser arguments, there is one overriding persuasion which would make me choose to limit my membership, financial and personal support to the local medical society—that reason is public relations.

It is my feeling that organized medicine on a national and state level, in the eyes of the average layman is:

1. The largest and wealthiest lobby in one nation's capital.
2. Too political.
3. Reactionary.

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est and most effective delegations to the AMA House of Delegates. The CMA delegation to AMA is doing an outstanding job and deserves the support of every doctor in California.

If we were organizing a new entity with three levels of responsibility and great diversity of opinion and philosophy among the potential members, it would be rational to allow membership in one or two components if this were the will of the majority. This, however, is a far cry from the factual situation.

The profession, indeed the nation, is engaged in a soul-searching debate concerning the future course of the health care system. The AMA is by far the most effective voice available to the members of CMA in the national arena. The next few years will be crucial in the efforts of doctors to influence legislation regarding national health insurance and the preservation of private practice. It will be a mistake, possibly a fatal mistake, if we undermine the influence of AMA by paving the way for a sizable exodus of CMA members.

MAURICE M. HASKELL, M.D.
Long Beach

If we feel that private practice of medicine is in the patient's best interest, then we must retain the freedom of practice we have and not succumb to the present political pressures of socialism to fragment and government control with the results of the decay of quality medicine for our patients.

The American Medical Association represents today the strongest voice of medicine. It is capable of wielding the greatest political influence because it speaks for the vast majority of physicians. We hear the argument that the AMA should be strengthened by making it more acquiescent to the demands of the medical profession by making AMA membership voluntary. We have such different political philosophies, however, that even today the AMA is accused by some of us as being too conservative, and yet, by others as being too socialistic. Obviously the AMA cannot represent all to the total satisfaction of all. However, we must not fragment now. This is exactly what the government planners want and are pushing for.

Our greatest strength will be acquired through unity, not only for manpower, but even more important for the dollar income to help with more effective public relations programs, committee meetings to establish guidelines, pamphlets designed for the general public, run an effective political machine. If one wishes to support the medical society it should be considered a three-level society with a choice of deciding whether or not to join—not to decide which level to join. Each society is in concert with the next level and should have our support.

We treasure our freedom, including our freedom to practice medicine according to our code of ethics and abilities and are already fettered by many government-imposed restrictions. If we are to avoid greater restrictions or government controlled medicine, we should be working to at least acquire financial support of all levels of our medical society. In this way we will have the unity and strength which we need to keep American Medicine free.

PREPARED BY A COMMITTEE OF THE ORANGE COUNTY
MEDICAL ASSOCIATION

At present, the public, the legislature and the news media generally assume that the American Medical Asso-

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4. Insensitive to changing socio-economic tides and times.
5. Not interested in the health problems of the people.
6. Greedy and interested more in its economic welfare than anything else.

I also believe that each individual has a great deal of respect for, concern for and love for his own physician. I believe the most good can be done at the local level.

I feel the AMA and CMA to be ineffective and money wasteful—in fact, intending to do good, but doing the opposite in the field of public relations.

I would, therefore, limit membership to the County Medical Association, limit personal support to the County Medical Association, and limit my financial support to the County Medical Association.

JOHN G. FAST, M.D.
Riverside
Riverside County Medical Association

The functions of a medical society or association should be the advancement of the science through education, coordination of community health needs, and perhaps assisting local physicians with some of the business problems of practice.

A medical association or society should not be a political union or pressure group. It should not be in the business of administrating and controlling the practice of medicine.

I believe that these unwarranted functions of medical societies can be eliminated at the local level by local effort. The state and national organization possibly can be changed after the local ones have been, but it may be simpler just to eliminate them.

This, of course, is an extreme view. If these views are not subscribed to by most people in medicine, they should at least allow those who hold them to be free to attempt to put them in practice. One should be allowed *freedom of choice*, certainly a basic concept upon which our society is supposedly based. The freedom involved here is one of choosing which organization, if any, one wishes to join. There should be no argument or discussion, the concept of freedom of choice is too basic.

ROBERT B. BUCHHOLZ, M.D.
Santa Rosa
Former Member, Sonoma County Medical Society

In considering the values involved in preferring AMA membership, the following are offered for consideration:

1. An organization comprised of members who freely belong requires a continuing sensitivity by the power structure to the needs and desires of that constituency. When the membership is mandatory, those vested with power may choose to ignore that subservience.
2. An organization based on voluntary membership speaks with greater authority for its numbered membership, and less likely to have divisive elements to distract from a professional image, and is more likely to provide a united front for more effective political muscle.
3. Elaboration of the many benefits of AMA membership by the proponents of compulsion begs the question. These benefits are more apt to be in greater abundance when the membership must be

ciation speaks for most doctors when it takes a stand. As a strong voice, speaking for a united profession, it has been effective more often than not. Now, however, there has risen an intense feeling among many doctors that perhaps the AMA does not represent the profession fully or well.

Physicians are bewildered by their changing role in society and frustrated by the ever increasing hostility that they encounter. They are hurt and angered by their loss of status and the decline in the traditional prestige of medicine. Aware of the erosion of the public image of doctors but unable to find any exact cause for their decline in esteem and power, they strike out at the most convenient target, the leaders of organized medicine.

Interestingly enough, both the right and left wings of medical opinion blame their leaders for failing them in a time of social change and inflation of health care costs. The liberal doctors claim that the AMA leadership is senile and arch-conservative, unable to keep up with the times, and therefore failing to meet our present problems. Conversely, the conservatives in medicine condemn the AMA and the CMA as being too liberal, feeling somehow that all would have been well if organized medicine had just taken a harder line and refused to go along with the government on any changes at all.

Both views fall short of reality, yet they are held by many of our profession. The referendum conducted in San Francisco last month showed that two-thirds of our doctors would prefer to choose voluntarily whether or not to join the AMA and CMA. Recent polls in San Diego and Los Angeles resulted in equally lopsided majorities in favor of voluntary membership in the state and national associations. At its Anaheim convention, the CMA voted to take a similar poll this coming September and it is reasonable to assume that the outcome will be for optional memberships. Although not all the doctors who vote for voluntarism will quit the AMA and CMA, a considerable number will. This will be a tragic mistake.

If ever medicine needed a united voice it is now. The next two to four years will doubtless see the beginnings of some system of national medical care and it is important that medicine has a strong voice in what type of system is initiated. We still think that the professionals in medicine are better qualified to plan and deliver medical care than politicians and bureaucrats. But if organized medicine speaks only in a fragmented Babel of voices, the leaders in Washington will design and implement their own plans.

A great many divisive voices are clamoring to be heard, all claiming that *they* speak for medicine. The various specialty groups and colleges each say that they are talking for their members. The Foundations for Medical Care have gone to Washington claiming to represent all the doctors in their areas. Groups such as the Councils of Medical Staffs, the Physicians Health Congress and the American Association of Physicians and Surgeons are busily recruiting. Then the American Hospital Association has its health plan which it presents as a blueprint for future medical care. Yet no matter what each group claims, it, in truth, represents only a segment of medicine.

Who does speak for medicine?

Today, only one organization, the AMA, speaks for all of medicine: surgeons, internists, general practitioners, psychiatrists, medical societies, teaching hospital staffs and university faculties.

courted than when the wedding is of the shotgun variety.

Polls recently conducted by several societies reflected a great majority favoring voluntarism. Compulsion advocates demean the intelligence of their colleagues when they dismiss these results as mere unthinking acceptance of the preferable word "voluntary," as opposed to "compulsion." They also ignore the growing disenchantment of many who regard the political representation of the private practice of medicine by the AMA as being out of tune with the desires and beliefs of its constituency, and the further belief that having a captive membership is not conducive to maintaining a responsible leadership.

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1. The voluntary way is the American way. Each physician should be free to make his own decision as to the advantages or disadvantages of membership in any organization. Compulsion is a concept out of our heritage of individual liberty in a democratic society.

2. For a profession which vigorously defends the principle of "freedom of choice" in health care, it is strangely incongruous that the CMA, with its "all or nothing at all," local society + CMA + AMA membership requirement, denies its individual members this freedom. Is compulsory membership fair to the physician and each of these organizations?

3. The argument that the AMA would disintegrate and become impotent without compulsory membership in California is specious. Only ten of the fifty state medical associations, including California, have mandatory AMA membership. Why should California physicians be denied their freedom to make a choice?

4. Voluntary membership without guaranteed dues would make such organizations more responsive to the desires and needs of their individual members.

5. Medical organizations with a voluntary, rather than captive membership can speak for their members with much greater authority. Government, insurance companies, unions, the press, etc. will listen with much more respect. Divisive elements detracting from a unified professional image would be much less likely.

6. Elaboration of the many benefits of CMA and AMA membership by the proponents of compulsion begs the question. Benefits are more apt to be in greater abundance when the membership must be courted than when the wedding is of the shotgun variety.

7. Compulsion tends to result in resentment and condemnation instead of the constructive, active support and courage by voluntary membership.

8. The legality of compulsory membership in medical associations has been challenged in several states. Should the CMA continue to expose itself to the indignity and poor public relations that could result from a possible suit for freedom of choice?

9. Specialty groups are assuming more and more of the burden of representing physician interests and are receiving increasing attention from socio-economic forces in society. Physicians, more than ever, are being forced to set priorities for their organizational commitments. Mandatory membership in two organizations (both the CMA and AMA) to maintain membership in another (county medical association) significantly interferes with the privilege of setting these priorities.

10. In a free-market economy, products sell on their

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Who will speak for medicine tomorrow?

Most probably and most unfortunately, a multitude of voices, none commanding enough power or respect to be heard and to guide the construction of a national health program.

PAUL SCHOLTEN, M.D.
San Francisco
President
San Francisco Medical Society

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There are many things in life which we do and accept. Some of these things we do willingly and some we do reluctantly, but we do them because in the long run they are for our good.

How chaotic would our medical education have been if some element of compulsion had not existed in medical school! We are now aware that this forced participation was beneficial to us.

We in Medicine should be able to learn from the history of the trade unions. They have become all-powerful because workers in all trades must belong to the union. Many workers, at times, find themselves in disagreement with their leaders but support them nevertheless. They have learned an all-important lesson, that only through a united voice have their goals been achieved.

Perhaps it is unfortunate that physicians are better educated and more independent than the average trade union member. Because of our intelligence and independence we question the actions of our leaders more often than we support them.

If ever Medicine needed a unified voice it is now. Many politicians, labor leaders and others will attempt to force some form of a national health program on the medical profession. Medicine still has some friends but if we have no national voice to speak for us, even these may be lost.

Our leaders, both state and national, have been criticized by some physicians as being too conservative. The average physician seldom takes the time or makes the effort to become knowledgeable about what the American Medical Association or the California Medical Association accomplishes each year for the benefit of physicians and medicine in general.

No physician in California is compelled to belong to the AMA, the CMA or his local medical society. We belong to our local component medical society because most of us want to be members of the family of medicine, the local society, the CMA and the AMA. It is only logical that this relationship should exist. There will always be some who want to share the benefits but refuse to accept the responsibilities of membership in any organization. Human nature being what it is, we all tend to prefer voluntary over compulsory activities. But if membership in our state and national association is on a voluntary basis, these organizations will in time lose membership and will no longer be an effective voice speaking for the physicians of California or the nation.

MEMBERSHIP POLL COMMITTEE
Humboldt-Del Norte County Medical Society



Every physician has the right to join organized medicine or not, but it must be all or none since this is the way the system is set up and the way it must continue in order to function properly. Those who advocate di-

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own merits. If the AMA and CMA represent real value, there need be no fear of a significant drop in membership were it voluntary.

11. A medical association cannot truly claim unity when its membership base is compulsory. Real unity of purpose and refusal to compromise principle characterize those organizations whose membership is voluntary. In the words of Thomas Paine, "Tis not in numbers but in unity that our great strength lies."

ALLAN K. BRINEY, M.D.
Los Angeles County Medical Association



The importance of having a single voice speaking for medicine cannot be disputed. The results and track record of the AMA over the past fifty years are deplorable. We are tired of being captive members of the AMA. We are weary of seeing increases in dues with decreases in effectiveness. We are weary of reading in the *AMA News* that the position of Medicine is strong, that we are sure to achieve our objectives, and that all is sweetness and light—while at the same time we read in the newspapers that we are getting thoroughly clobbered.

The AMA once stood at the forefront of progressive thinking and socially responsible action. Witness its support of the Pure Food and Drug Act and our present system of medical education. The AMA is limited now by its inability to communicate its ideas to its members or the public. Organized medicine (AMA) has yielded the initiative to other parties. Many of us are convinced that the new generation, plus many of the older physicians, will decide to let the AMA go its own way, mainly because changes will never be accomplished from within.

In our own Society we can stand up and be heard. The AMA delegates are elected by an archaic system of rubber-stamping a nominating committee's selection. This is the same type system the Congress used to select Senators until 1913. If the slow moving Government could enhance the democratic process by handing the choice of Senators over to the people why must the AMA continue to preserve antiquated methods? Too often our own CMA delegates tell us what is good for us and pay minimal attention to our complaints. If we have so little influence on our own delegates, what then can we expect from our AMA delegates?

The fragmentation that is occurring in medicine can be laid at the door of the AMA. It has steadily lost power and territory to others in the health field. Currently the AMA has less than friendly relations with hospitals and medical schools and the Federal and State governments. The AMA leadership continues to be arch conservative; negative in approach and thereby failing to clearly see the surging tide of health problems needing solution.

No reforms appear on the horizon. The AMA demonstrates no realization of the self destructive course it has pursued in the past.

Resignation from both CMA and AMA may not be the solution. However, the option to do so must be present. Massive resignations may bring the juggernaut to a halt. This could stimulate both organizations to examine their posture of negative vigilance and a desire to change to a vital organization sharing problems with their members.

The option for membership must remain with the member, he should not be forced to belong. Membership in both CMA and AMA should be based upon a desire for membership. This desire for membership can only be nurtured and fostered by demonstration of concern

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vided membership are trying to abdicate their responsibility, both financial and political. Medicine must have a united voice and those who are advocating separate membership, because they disagree with the present leaders and policies, can, if they desire, use their efforts within the existing framework to change leaders and policies. Non-participation by the dissident is much less effective in changing the course of organized medicine than is intelligent dissent within the organizational framework. Advococation of separate membership for financial reasons is absolutely unacceptable.

R. W. CLETSOWAY, M.D.
President
San Luis Obispo County Medical Society



In the very near future you will be invited to participate in a poll on an issue before the CMA which could well have profound effect on all of organized medicine for many years to come.

The issue is simply whether or not membership in your county medical society should require membership in the CMA and AMA.

I wish I could say the answer to this were as simple as the question itself, but it indeed is not. Unfortunately in discussing this issue, the words, compulsory versus voluntary, are being interjected, and most of our responses would be immediate and obvious; for as individualistic as most of us are, the word, compulsory, carries a connotation which is unacceptable. The consequences of making membership in the CMA and AMA voluntary, however, should be carefully considered.

It is certainly true that there have been many times when these organizations have not truly represented me, and possibly you, in our political, social, and medical philosophy. The same could also be said occasionally for our own county medical society. Regardless of this, the fault for some of this situation lies directly with many of us who have abdicated our responsibility to our own professional association, preferring to leave it for someone else to represent us. Sometimes not truly our representative, sometimes not really our best foot forward, and for some of this, we must accept the inevitable consequences.

This does not mean, however, that total rejection of our present representative system is a better solution, rather, the strengthening of our democratic process to better represent us and unify us as an organization which can truly be the voice of organized medicine.

Therefore, I would propose that you carefully consider this very important issue and perceive it not as compulsory or voluntary membership in the AMA and CMA, but as supporting organized medicine or not supporting organized medicine, which can, and will, represent you well if empowered to do so. Belong or don't belong, this is your decision, but don't destroy your association at a time when a strong voice for American medicine is so sorely needed.

There are those who would delight to see you divided. In Britain it was division of the specialist and the generalist. In this country it has taken other forms, but make no mistake, the objective is the same, and I would again implore you to weigh your decision carefully.

JAMES R. HANSEN, M.D.
President
San Mateo County Medical Society

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for the welfare of their members and not by the beefing up of their public relations department to buy a better image.

MEMBERSHIP POLL COMMITTEE
Humboldt-Del Norte County Medical Society



We feel that in an isolated rural area membership in these organizations be separate and voluntary. It is important that an organization of doctors be operative and functioning to provide an interchange of ideas for problem solving, to provide a framework for utilization review and to provide also a framework for review and/or disciplinary actions if such should be necessary for the doctors of the group. If some isolated member of the county medical society should decide he should not become a member of the CMA or the AMA or both of these organizations, it would presently be impossible for him to remain a member of the local county society. Without his membership the local society would be less powerful to take action or to communicate appropriately with such a doctor. It is the feeling of this society that, should membership in the three organizations be voluntary, the strength of the organization would be increased because the membership would be composed of those who are interested, rather than by a coercive mandate.

Another side of the argument by those in favor of combined membership: This certainly is a time in history when medical practice and the medical profession itself must be united and it is the feeling on the part of some that should the membership ruling be changed there is the possibility of a smaller membership with less income and less power in dealing with governmental problems and issues on the scene of today.

DAVID G. DAEHLER, M.D.
Susanville
Secretary, Lassen-Plumas-Modoc-Sierra
Medical Society

Training Groups, Encounter Groups, Sensitivity Groups and Group Psychotherapy

LOUIS A. GOTTSCHALK, M.D., E. MANSELL PATTISON, M.D., AND
DONALD W. SCHAFER, M.D., *Irvine*

■ *Descriptions and comparison of group therapies and the new group procedures (training groups and sensitivity groups—an outgrowth of the so-called Laboratory Movement methods of the mid-1930's) have been provided for the better understanding of non-psychiatric physicians. A group leader must have proper training and must help his group in its search for its avowed goals, whether he is a group therapist, a sensitivity trainer, or anyone else interested in utilizing group processes.*

Those goals are either the therapeutic benefit of the individual, as defined in group psychotherapy, or a better understanding of how one functions in groups, as in T-groups or the other group processes in the area of sensitive living. All group situations contain powerful tools which must be handled with proper respect. When so handled by experienced leaders, the individuals involved can achieve their goals in these group experiences.

IN RECENT YEARS intensive group experiences have evolved in so many different directions that many of them are difficult to define. The non-psychiatric physician can neither keep them straight nor be expected to approve those which receive adverse notoriety. Some of the most important of

these are training groups (T-groups) and sensitivity groups which have grown out of what is referred to as the Laboratory Movement of the 1930's. These have a different approach and a different aim from the conventional group therapies, although both utilize a group situation. The purpose of this paper is to try to clarify for physicians the group situation in both of these areas as it now stands so that the modern doctor can intelligently answer the questions that his patients might ask him about what can be expected if participation in one of these groups seems advisable.

From the Department of Psychiatry and Human Behavior, University of California, Irvine, California College of Medicine.

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The Group Psychotherapies

We will not be overly explicit here about the group therapies, for the word *therapy* implies that the patient is there for his own sake to correct something within himself, usually some emotional problem which he and the professional therapist both define as part of his complex of symptoms. He is a patient. These therapies make use of the group setting to give the patient some kind of a sought-for change which will help him in his efforts to get well. To review briefly, group therapy can be divided into the same three categories into which all of the psychological therapies fall—supportive therapy, re-educative therapy, and insightful therapy. These terms are self-explanatory. All group therapies are handled by or under the direction of a leader—a psychiatrist, a psychologist, a psychiatric social worker, a religious counselor, or people who are working under the direct supervision of these mental health personnel. In more recent years this list has included psychologically-oriented physicians, especially those dealing with specific kinds of groups, such as ones aimed at helping the obese or instructing women in natural childbirth. These professionals have had an educational experience which instilled in them adherence to a rather extensive ethical and legal code.

Group therapies can further be differentiated as being either heterogeneous or homogeneous. For instance, groups can be made up mostly of depressed, middle-aged housewives, of couples with marital problems or of both. Also, groups can be open-ended, that is, continually admitting and discharging patients, or closed and limited. More recently, in community mental health programs, psychiatric aspects of treatment groups can be crisis-oriented.

Sensitivity Groups, Training Groups, And Marathon Groups

Let us here provide a typical set of relevant definitions of the new kinds of intensive group processes.¹

The pivotal aspect of the new group processes is the laboratory movement or the training laboratory. A *training laboratory* is an educational procedure which aims to create a situation in which the participants, through their own initiative and control, but with access to new knowledge and skilled professional leadership, can ap-

praise their old behavior patterns and attitudes and look at new ones. A laboratory experience recommends a temporary removal of the participants from their usual living and working environment where any attempts to re-evaluate attitudes or experiment with new behavior patterns might involve risks and possible punishment. It provides a temporary artificial supportive culture (hence the designation *laboratory*) in which it is safe for the participants to confront the possible inadequacies of their old attitudes and behavior patterns and to experiment with and practice new ones until they are confident in their ability to use them. The assumption of the laboratory method is that skills in human interactions are best learned through participation in events in which the learners, themselves, are involved. The training activities, therefore, are social experiences in which the trainees take part and then reflect upon their patterns of participation. Essentially, the laboratory scene provides a location for experimental learning.

Sensitivity training is any of a set of experiences, including but not restricted to the training group, attempting to help each participant to recognize and to face in himself and in others many levels of functioning (including emotions, attitudes, and values), to evaluate his behavior in light of the responses it elicits from himself and others at these various levels, and to integrate these levels into a more effective and perceptive self. The basic data for learning come from the participants themselves, and from their immediate experiences within the group as they interact with each other in the effort to create from their own resources a productive and meaningful group. The experience is designed to provide a maximum opportunity for the participants to expose and analyze personal behavior and group performance, to learn how others respond to their behavior, and to learn effective personal and group functioning.

Marathon group is a term used to describe a sensitivity training group which meets continuously for periods of time ranging from 12 to 36 hours. The purpose of this technique is to heighten the impact of sensitivity training by means of continuous uninterrupted interactions which are being generated within the group. Some marathons have been used in weekend laboratories, where the total amount of time available was relatively short, as a device to move

the group in a single day to a greater depth of involvement and group interaction.

The *trainer* is the experienced leader or facilitator within a sensitivity training group who serves as a resource to the group. Since the primary social learning data for the participants will come from their own involvement with each other and with the group, the role of the sensitivity group trainer is different from that of the usual role of an educator or leader. He cannot assume the role of the expert, controlling and directing the group, without making the group dependent upon him, thereby undercutting the experience of group responsibility and participation which is supposed to be the primary source of learning data. The trainer, therefore, is supposed to serve more as a facilitator than a direct source of information, helping the group to make its own decisions and to use its own resources. He does this by calling the attention of the group from time to time to the behavior which is being exhibited and the relationships which are emerging in the group, and by helping the group to clarify its own goals and procedures. The trainer focuses primarily upon the "here and now" events and relationships which have been experienced within the life of the group.

Origins of the Laboratory Movement, T-Groups, and Sensitivity Training

With these brief descriptions of the new group procedures, we will now sketch out the history of these activities. These groups grew out of a completely different focus than that of the group therapies. From the time of Aristotle until the late nineteenth century, psychology was the study of individual minds.² Group interaction and interpersonal relations were not considered in the province of psychology, and the theories of social interaction in the psychological frame of reference were theories of individual reactions. Toward the turn of the century, some workers began to focus upon crowd psychology for the first time.³ During the 1920's social scientists began to study social interaction in normal social groupings with the conviction that the solution to social problems could thereby be facilitated. In the 1930's, Kurt Lewin developed his now famous field theory and began to implement action research as an approach to social change.⁴

The direct development of the training laboratory came from the collaboration of three men: Leland Bradford, Ronald Lippitt, and Kenneth Benne.^{5,6} All three had an educational background in psychology, experience in working with community educational projects, and involvement in numerous national projects dealing with major social problems related to human relations. They had been exposed to J. L. Moreno's methods of psychodrama,⁷ and had experimented with various role-playing procedures in community educational projects. In the summer of 1946, Bradford, Lippitt, Benne, and Lewin undertook a project to train a group of community leaders to deal with interracial problems. In addition, they planned to use this project as a means of studying their methods of group discussion as an educational procedure.

The T-group was born almost by accident during this summer project. Research assistants had been assigned to each discussion group to record the interaction and report their observations to the research team. The group members requested and were also allowed to attend informally these feedback sessions. The educational-research team observed the interest and enthusiasm generated in these sessions among the group members and immediately grasped the potential for group self-evaluation as a means of teaching the development of effective democratic group processes that could be applied to community group action. With this experience, the seminal ideas of the laboratory movement were developed, focusing on a new method of training people from communities in the process of democratic group formation. The new method was to be a laboratory for self-examination of group process. (For historical notes see references 5,6,8.)

Education has been one of the major institutional bases for this method, even though only a minority of schools participate widely in group training laboratories for their students. Human relations training in the classrooms exemplifies this tradition.^{9,10} The most firmly established institutional basis is in the field of business and industry where there is a concern for the improved function of work groups. The training movement has focused both on the "sensitization" of leaders to their impact on their work teams and task-oriented learning experiences for teams of persons who work together.^{11,12} Although social action was the initial concern of the founders

of the movement, it was not until the late 1960's that this focus really evidenced itself. This training movement as a therapeutic method for "normals" has been one of the strongest and most popular and prestigious areas of the laboratory approach, a seedbed from which have sprouted many variants, such as marathon groups, encounter groups, sensitivity groups, and personal growth laboratories.¹³

Finally, the training movement has continued to provide impetus for the scientific study of group dynamics, group process, leadership functions, decision making, and conflict resolution.¹⁴ However, the pioneers in the early laboratory movement with research orientations from the fields of psychology and sociology have, for the most part, departed the scene and transferred their research to the more scientific arena of their respective disciplines, leaving the laboratory movement as a predominantly clinical and applied discipline.^{15,16}

When one surveys the small monographs published by the National Training Laboratories, a definite trend is discernible.^{9,17-21} In the 1940's the movement expressed the concern for a method of teaching American communities techniques for participatory democracy. Group process and task-oriented group function dominated the scene. In the 1950's the concern shifted to individual growth, self-knowledge, and actualization and maturation; and the similarities between group psychotherapy and the sensitivity groups became blurred, so that today it is difficult to talk about one without talking of the other at the same time. Finally, from the mid-1960's on, there has been renewed interest in the original aims of the laboratory method as evidenced in *The Journal of Applied Behavioral Science* which was begun in 1965 as a vehicle for critical re-evaluation of this field.²²

The Laboratory Method, including training groups and sensitivity groups, at this time is a movement of interested and concerned people who have not as yet acquired even a hybrid professional status. This is partially due to a lack of uniform ideological bases and goals, although most aspects of the Laboratory Method spring from the field of social psychology. Schools of education and schools of business administration represent the major sources of institutional and professional support. The groups have remained peripheral to mental health professional training.

Unfortunately, without an identifiable discipline there have been no norms for performance and no explicit forums of evaluation.

The T-Group Procedure

The typical T-group may now be examined more specifically. The participants are, preferably, "normal" people with good personality integration and coping skills who can readily learn from experience. This group works toward a heightening of interpersonal skills, a sharpening of interpersonal perception, an increase in self-awareness and "authenticity" of life experience. The T-group "trainer" or leader functions more as an expeditor or catalyst than an authority or power figure. He may, in the course of the T-group, become fully assimilated into the group, thereby abdicating his attributes as a leader and giving up his position of responsibility toward the group. Hence, the designation "leaderless" for some kinds of T-groups.

The T-group is a relatively short term activity. It meets for several hours daily for two weeks, although at times the span is lengthened to a month. Sometimes such a group takes other directions such as a group of the marathon type, which may last 12 to 36 consecutive hours. The T-group may be made up of people who are related by virtue of working together or it may be composed of people who are strangers to one another. Group psychotherapy uses the group process as a method to help a patient correct an emotional problem, whereas T-groups were developed to instruct so-called "normal" people about their behavior in groups. In 1964, Jerome Frank²³ was able to make fairly clear distinctions between the T-group and the psychotherapy group. Training was distinct from therapy, as Frank saw it, even though there was some overlapping. In his view, therapy took up where training left off. As was mentioned earlier, this view is no longer so easy to maintain, other than on a theoretical basis.

In further describing the T-group, let us examine the actual procedures. First, T-groups present a minimal number of cues to participants in the group on how to proceed. The new T-group member is usually not advised that he will be expected to learn what he wants without guidance. Instead, he finds himself having to rely on observation of the behavior of himself

and others in this group in order to find a semblance of organization and order in a life situation without a *modus operandi* and a definitive leader. The trainer functions not to provide the operational guidelines, but to point out and help the group members become aware of what is happening. In their efforts to supply structure where it is absent, group members vie with one another to propose a program of operation and organization and rules of procedure; however to do so, each group member falls back on his personal experiences of how groups should function, and each participant attempts to set up the organization of the group in a way that fits his experience, thereby inadvertently attempting to reproduce in the T-group his typical role and function in other groups. At the same time, other members of the group are doing the same thing in their own particular style. The self-centered individual, the manipulator, the person who neglects to keep his fingers on the pulse of each individual in the group, the rebel for rebellion's sake, the peacemaker, the person who characteristically stays on the sidelines—these personality types and others reveal themselves to the group. If they are attuned to the feedback available from other group members, they will be offered a reflection of themselves as they perform in their customary roles. The reflection is not infrequently distorted rather than clear and sharp, for the reflecting surface of these human mirrors is roughened and distorted by the perceiver's own opinions, values and emotional conflicts.²⁴

Uses and Advantages of The T-Group Method

The T-group provides a vehicle for teaching the importance of interpersonal relations in natural group functioning. Rather than through didactic description, the T-group teaches through experience. An analogy might be made with the teaching of arithmetic. The teacher can do a problem on the board, but the student does not learn the arithmetical maneuver until he has actually solved a number of similar problems for himself on his own paper.

The T-group provides a means of sharpening perceptual skills—of recognizing interpersonal perceptual distortions, learning ways to check out interpersonal receptions, and learning how to correct interpersonal perceptions. A corollary is

the learning of one's own functioning in a group: seeing the role one plays vis-a-vis others, how one distorts the presentation of self to others, and obtaining corrective feedback. The T-group teaches people how they communicate with others, the variety of modes of interpersonal communications, and how to increase the effectiveness of communication, while decreasing the "noise" in the communication system. It provides a degree of "experiencing isolation," similar to the isolation of psychotherapy, which may enable participants to test out different modes of interaction and broaden their repertoire of human relations skills.

The T-group and related laboratory exercises have provided theory and method for effective intervention in organizations. This may range from natural community groups (churches) to community action groups (urban renewal), service organizations (YMCA), and business and industry (Shell, Esso, Bell Telephone). The human-relations emphasis in the T-group and laboratory method provides a method for nurturing human growth that may be incorporated into our educational structure to counter-balance many of the dehumanizing elements of American culture and particularly the mechanistic elements of the American school system.²⁵

The laboratory movement has given impetus and support to the scientific study of group function, leadership, and function of different types of groups, and these have received little emphasis in the clinical professional conventions. It has introduced many innovations in group interaction that may have clinical applicability: brief therapy groups, intensive group experiences, use of nonverbal interaction methods, refined use of group process analysis, and increased effectiveness of task groups.

Criticisms of the T-Group Method

Some of the basic assumptions that seem to have evolved in T-groups are open to criticism.²⁶ One of these is that the group should be and can be trusted. It is also implied that T-group trainers have not only the sanction and blessing, but the stamp of approval, of the National Training Laboratories or some other qualified training organization as wise, experienced teachers of group dynamics, counselors, and emotionally well adjusted persons. Unfortunately, in too many instances, the group trainers have not had much

organized professional preparation. Each trainer goes through several T-groups himself. This may eventuate in the selection of the more extroverted, self-confident and socially proficient persons to be future T-group leaders themselves. It does not guarantee either that the trainer has emotional or intellectual acumen with respect to recognizing and preventing the development of disruptive emotional breakdowns in T-group members or that he has the ability to examine such developments critically and discover his role in permitting or inciting them to occur. The trainer for the most part is free to hold any theoretical orientation he chooses. He usually appears to disregard or deal in a desultory fashion with the effect of extra-T-group contacts with group members during a series of T-group sessions. These extra-group contacts may, however, influence group dynamics. The typical trainer emphasizes the importance of recognizing emotions, but often there are no attempts by the trainers to question the appropriateness or rationality of emotional reactions. Many trainers, while defining the training group as non-therapeutic and predominantly educational, proceed to try to effect attitudinal and behavioral changes within that group.

T-groups set up a powerful emotional situation that is capable of evoking many kinds of dramatic reactions in the participants. Sometimes these reactions involve more than a mild exaggeration of the typical psychopathological traits of group members. For instance, in one T-group of 11 participants (and two trainers) there occurred: one borderline, acute, psychotic withdrawal reaction, two severe breakdowns with acute anxiety, crying and temporary departure from the group, one sadistic and exhibitionistic behavior pattern and two pronounced reactions of isolation and withdrawal—in all, six obviously acute pathological emotional reactions. People who are very active in group work of this kind assert that the incidence of psychopathological reactions of this magnitude is unusual, and that temporary severe emotional reactions may be a necessary part of a growth process. But we believe that a situation that can evoke pathological personality reactions of these types and intensities is, indeed, worth examining more closely even though it undoubtedly promotes the self-esteem and sense of achievement of most participants, for they report feeling at least as well and

comfortable if not better than before the T-group experience.

The T-group is as good or as bad as its trainer, the selection of participants, and the contracted purpose for the group meetings. The lack of the leader's clearly defined responsibilities is often felt as somewhat reprehensible by men of the medical profession. (Responsibility for the group is regarded as an overall ethical issue, not the style of leading the group by not giving directions.) Although the aims of the T-group may be beyond criticism, the results often seem to be a "game of hit-and-run." In this way it may foster a sense of pseudo-authenticity and pseudo-reality in which the participant can learn to be angry and to scream at people, and to do other things which he would not do in his normal living situation where he would reap the consequences of his behavior. Patterns that are considered "good" in T-groups may be completely inappropriate to a participant's real life circumstances. Exposure and frankness, attack and vulnerability may become premium values. Often too little attention is paid to the necessity for support and nurturance. Human foibles, inadequacies, and the normal range of variation in life style may be given short shrift. Individual tolerances to stresses and frustrations are often not considered. The result sometimes leads to a participant becoming a person who can take anything a group dishes out.

When groups are carried to the extreme of disregarding consequences of individual actions within that group, personal narcissism is often fostered and self-analysis and reflection are forgotten. In one professional work-team, for example, the members were instructed to tell, "how they really felt about each other." The members successfully "told off" their chief in the T-group. The result was total disruption and ineffectiveness in their business situation thereafter. The trainer had ignored completely the goal of helping this professional team to work together. It is suggested that each trainer very carefully size up the "contract" he makes with any group. He has a responsibility both to a group as a functional unit and to individual members. Neither a work group nor its members should be hurt. A group of people can be tyrannical and destructive just as they can be beneficial and supportive.

Recent developments in T-groups have led to some innovations in teaching self-awareness.

These have involved actual physical contact, such as wrestling, lifting, and touching each other, which raises a number of theoretical, technical, and ethical issues which will not be discussed here. Regardless of their possible validity, they do represent a shift from the avowed goal of the T-group as a democratic group educational experience. Another questionable assumption in the T-group situation is that all members learn at the same rate and that, therefore, the length of the T-group situation can be a relatively minor variable. Pattison²⁷ has shown, in the context of group therapy, that such time variables need considerably more careful investigation. The assessment of T-groups results has not considered seriously the deleterious effects of adverse countertransference reactions in therapists, especially nonpsychoanalytic psychotherapists. (See the review of Orr²⁸ of the rationale for the preparatory psychoanalysis of the student psychoanalyst.) The idea that a T-group experience will always be profitable must be questioned. However, the liabilities described above are not intrinsic deficits; rather, they are deficits of training, experience, clarity, and precision of goals²² and can be avoided. Leaders within the Laboratory Movement are addressing themselves to the task.

Of more concern are the peripheral and derivative products of the Laboratory Movement. We are alarmed about the people who have picked up bits and pieces of this movement, without the democratic concerns of the originators, without the clinical experience of the early leaders, without even the informal communicative guidelines that tend to keep professionals within a self-corrective framework. There is often no continuing inquiry of a self-critical and self-evaluative nature.

It is perhaps paradoxical that despite the enthusiasm that the Laboratory Movement has fostered, its practitioners have not fully realized how powerful are the tools they have developed. Therefore, the enthusiasm may not yet be tempered with the respect that these tools be rightly used.

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Information

The Selective Service System and Physicians

L. S. GOERKE, M.D., *Los Angeles*

A NATIONAL PROGRAM was developed several years ago which provided the younger physicians most liable for selection for military service or substitute service, the opportunity to plan the time for service consistent with their residency training, and sometimes consistent with their career objectives. This was the Berry plan, the Armed Forces physician's appointment and residency consideration program. The program was planned to meet the replacement needs of the Armed Forces as other physicians completed their tour of duty, and to meet the needs for Board-certified specialists in major installations of the Armed Forces. At approximately the same time, special incentive salary scales were established that were higher than those for other professional groups required in the Armed Forces.

The military requirement for health manpower stimulated many registrants to seek appointments in the United States Public Health Service under the Commissioned Officer Residency Deferment Program. However, the number and types of assignments with the USPHS were restricted somewhat with the last congressional extension of the Selective Service legislation. The number of positions planned and budgeted for these programs are not being filled under the voluntary program. The fact that the Selective Service has had no call for physicians from the Armed Forces for the past

two years has not, apparently, provided the stimulus to physicians to volunteer for the Berry plan of commissioned deferment for residency training. Therefore, activation of a special call for physicians has become necessary to help meet national needs.

The Special Call No. 46 for physician manpower for the Armed Forces is listed as follows:

Time Phase	Doctors of Medicine	Doctors of Osteopathy	Total Physicians	Percent
July 1971	584	30	614	38.2
Aug. 1971	469	24	493	30.7
Sep. 1971	153	8	161	10.0
Oct. 1971	146	7	153	9.5
Nov. 1971	48	2	50	3.1
Dec. 1971	89	4	93	5.8
Jan. 1971	42	2	44	2.7
Total	1,531	77	1,608	100.0

The quota for California is usually 10 to 13 percent of the national call and about equally divided between Northern and Southern California. The greatest impact of the call will fall on the metropolitan areas of the state in view of the general philosophy and policy documented by the National Security Council with respect to deferments of physicians, dentists, and allied specialists. The Security Council recommends that certain doctors who are essential to and irreplaceable in their communities be deferred if a replacement cannot be found by the community involved in the time allotted by postponement of induction. In carrying out this policy, the national director and the state director of Selective Service have recommended that local boards review the situations of doctors of medicine and doctors of osteopathy who are under the impending call (and probably, eventually, all who are in 1A classification) for evidence concerning the essentiality of the doctor to the community. A safe premise is that all physicians, who are in a 1A classification, are available under an induction order and, therefore, are vulnerable if there is no documentation in the physician registrant's file with the local boards as to his essentiality to the community. More specifically, "a physician, dentist or allied specialist may be considered as essential in the community only if he is *directly involved in patient care* and his removal from the community would result in an extreme shortage of an especially critical community service where a replacement cannot be found by the community involved in the time allotted by a postponement of induction." Many decisions

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will need to be judgmental since "community," "extreme shortage" and "critical community service," and "direct medical care" are not defined. Because of the lack of definition, a great amount of objective and analytical judgment will be required, and the advice and guidance of the county medical association and the state medical association may be needed. A procedure exists for review

by state medical advisory committees, which in the past had systems to obtain advice from senior physicians and other sources in almost every county in the state in an organized and systematic manner.

The majority of the physicians for this call will come from the metropolitan areas and some hospitals will lose residents.

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PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H., Director, State Department of Public Health

Soft Contact Lenses

RECENTLY THE U.S. FOOD AND DRUG Administration (FDA) approved a new drug application for a Bausch and Lomb plastic contact lens. Because applications on similar products from other companies are pending and may also be approved, it is advisable to clarify the status of soft contact lenses.

A soft contact lens is considered a new drug under definitions of that term both in Federal and California regulations. Federal and State laws require adequate testing of such products before marketing by the supplier. The State Department of Public Health enforces the Sherman Food, Drug and Cosmetic Law in California, including investigational new drug (IND) exemption requirements.

The reason for the IND procedure in the case of plastic contact lens is that soft lenses are hydrophilic. There are inherent hazards from leaching of such constituent lens material as residual plasticizers, oxidants, sensitizers or irritants and other chemicals. Concentration of retained solutions and the difficulty in establishing and maintaining sterility may also constitute dangers. There are some problems of uniformity in composition and in maintenance of shape, form and refractive properties which affect suitability for use in the human eye.

Under the State food and drug law, selling,

dispensing, applying or giving away in California any soft contact lens which is not the subject of an effective new drug application (or IND) is a misdemeanor. We are confident that physicians will cooperate with us in protecting the public's health by observing the applicable Federal and State regulations concerning investigational new drugs.

Patients should be supplied with such products only when safety and efficacy have been assured by appropriate testing carried out under the IND procedure. Each supplier who has an approved new drug application (NDA) or an investigational new drug application (IND) on file with the FDA has an NDA or IND number and should supply it to physicians when they purchase the lenses. Physicians may prescribe only soft lenses obtained from suppliers who have approved new drug applications (NDA) in effect. To prescribe soft lenses which are being tested under investigational new drug applications, the physician must serve as investigator in connection with a supplier's claimed exemption for the investigational new drug. In this case, he will be asked by the supplier to provide a statement that he is an investigator with appropriate qualifications to participate in such tests and he will be requested to acquire data suitable for filing a new drug application.

To prevent exploitation during the investigation, both federal and state regulations prohibit commercialization in connection with tests of investigational new drugs and devices such as soft contact lenses.

For further information, physicians may call the State Department of Public Health, Bureau of Food and Drug, (415) 843-7900, extension 426.

In Memoriam

BOLENDER, MELVIN C., Walnut Creek. Died May 23, 1971 in Oakdale of ruptured sclerotic abdominal aortic aneurysm, aged 76. Graduate of University of Nebraska College of Medicine, Omaha, 1930. Licensed in California in 1930. Doctor Bolender was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

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DEMANDANTE, PRIMITIVA D., Wilmington. Died June 6, 1971 in Los Angeles of massive cerebral hemorrhage, aged 58. Graduate of University of Michigan Medical School, Ann Arbor, 1942. Licensed in California in 1943. Doctor Demandante was a member of the Los Angeles County Medical Association.

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DOW, JULIAN NEAL, Beverly Hills. Died June 6, 1971 in Los Angeles of bronchopneumonia, aged 78. Graduate of Bennett College of Eclectic Medicine and Surgery, Chicago, 1915. Licensed in California in 1919. Doctor Dow was a member of the Los Angeles County Medical Association.

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FARRAND, RODERICK C., Malibu. Died April 17, 1971 in Malibu of cardiovascular disease, aged 59. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1949. Licensed in California in 1949. M.D. degree from California College of Medicine, 1962. Doctor Farrand was a member of the Los Angeles County Medical Association.

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FOSTER, HARRY EMERSON, Berkeley. Died June 26, 1971, aged 89. Graduate of the University of California Medical School, Berkeley-San Francisco, 1908. Licensed in California in 1909. Doctor Foster was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

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GOOSEBERG, JERRY, Canoga Park. Died June 13, 1971 in Panorama City of Hodgkins Disease, aged 34. Graduate of Jefferson Medical College of Philadelphia, 1962. Licensed in California in 1967. Doctor Goosenberg was a member of the Los Angeles County Medical Association.

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GORDON, ASHER T., San Francisco. Died June 12, 1971 in San Francisco, aged 54. Graduate of the Johns Hopkins University School of Medicine, Baltimore, 1941. Licensed in California in 1943. Doctor Gordon was a member of the San Francisco Medical Society.

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GREENING, PAUL K., Fresno. Died June 17, 1971 in Fresno of heart disease, aged 49. Graduate of University of Utah College of Medicine, Salt Lake City, 1950. Licensed in California in 1968. Doctor Greening was a member of the Fresno County Medical Society.

HAAS, SYLVAN LEWIS, Inverness (Marin County) and San Francisco. Died June 21, 1971 in Kentfield, aged 88. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1908. Licensed in California in 1910. Doctor Haas was a member of the San Francisco Medical Society.

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HEBARD, FLOYD MALCOLM, Glendale. Died May 22, 1971 in Glendale of heart disease, aged 73. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1925. Licensed in California in 1925. Doctor Hebard was a member of the Los Angeles County Medical Association.

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MCCOWIN, JOSEPH AARON, Los Angeles. Died January 4, 1971 in Los Angeles, aged 46. Graduate of The George Washington University School of Medicine, Washington, D.C., 1953. Licensed in California in 1954. Doctor McCowin was a member of the Los Angeles County Medical Association.

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MERRITT, ROBERT EDWARD, Redwood City. Died June 23, 1971 in Redwood City of cancer, aged 63. Graduate of Cornell University Medical College, New York, 1935. Licensed in California in 1936. Doctor Merritt was a member of the San Mateo County Medical Society.

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THOMPSON, ROLAND LEWIS, Burbank. Died December 23, 1970, aged 76. Graduate of Northwestern University Medical School, Chicago, 1921. Licensed in California in 1921. Doctor Thompson was a member of the Los Angeles County Medical Association.

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WINFIELD, MARK EDWIN, Los Angeles. Died June 3, 1971 in Los Angeles of Hodgkins Disease, aged 42. Graduate of Columbia University College of Physicians and Surgeons, New York City, 1955. Licensed in California in 1957. Doctor Winfield was a member of the Los Angeles County Medical Association.

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BOOK REVIEWS

CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

CONGENITAL AND PEDIATRIC GLAUCOMAS—Robert N. Shaffer, M.D., Clinical Professor of Ophthalmology, University of California School of Medicine, San Francisco; and Daniel I. Weiss, M.D., Assistant Clinical Professor of Ophthalmology, New York University School of Medicine, New York City. The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1970. 221 pages, with 253 illustrations and 3 color plates, \$20.50.

Congenital and Pediatric Glaucomas by Shaffer and Weiss is an excellent manual of instruction on this complicated group of diseases. The text is clearly written in a way which puts forth the essential information without undue detail. The authors have assumed no previous knowledge of the subject on the part of the reader, yet the didactic material is in no sense oversimplified.

The text is copiously illustrated by both photographs and diagrams. Whereas the photographs are not uniform in quality, and many of them have actually been borrowed from Becker and Shaffer's earlier book, *Diagnosis and Therapy of the Glaucomas*, (2nd Edition, St. Louis, C. V. Mosby Co., 1965), they serve admirably to illustrate the various sections. In my opinion, that function is not particularly well served by the color plates. The latter added little to my education and undoubtedly increased the expense of this small book unnecessarily.

The book has been divided into appropriately arranged chapters which cover the various sub-topics beautifully. The chapter on classification and fundamental considerations begins with a clear set of definitions. It also contains excellent diagrams of fundamental processes connected with tension increases in the eye. The chapters on the phakomatoses and the mesodermal anomalies are particularly well written; they summarize much of the currently established data on a number of syndromes which might ordinarily appear confusing to the casual reader. These sections will be particularly valuable for the pediatrician and for those ophthalmologists who have relatively little occasion to see children. The section on therapy is divided into two chapters: one on medical treatment, the other on surgical treatment. Both are well presented, although the chapter on surgical therapy is certainly more extensive. Here again, the photographs and diagrams are very helpful.

The book is well indexed, and this will also contribute to its usefulness as a manual for the busy ophthalmologist or pediatrician. For all these reasons, I recommend the book highly; and I think that most ophthalmologists will find it a useful and up-to-date text.

G. RICHARD O'CONNOR, M.D.

OPHTHALMIC PLASTIC SURGERY—Fourth Edition—Sidney A. Fox, M.S. (Ophth.), M.D., Clinical Professor of Ophthalmology, New York University School of Medicine; Visiting Ophthalmologist, Bronx, V.A. Hospital, Goldwater Memorial Hospital and Hospital for Joint Diseases and Medical Center. Grune & Stratton, Inc., 757 Third Avenue, New York, N.Y. (10017), 1970. 590 pages, \$29.75.

Residents and practitioners of ophthalmology have used the first three editions of *Ophthalmic Plastic Surgery* as prime sources of basic, practical information. Like the earlier editions, the latest is well illustrated, clearly written, and soundly grounded in the substantial personal in-

terest and experience of Dr. Fox. The book is clearly didactic rather than encyclopedic. Based as the text is upon the author's own experience and preferences, many variations in surgical approach, particularly some relatively recent techniques, are not covered. Some omissions, such as the absence of differential section of the facial nerve from the discussion of treatment of essential blepharospasm, are unfortunate. While those whose favorite operations have been omitted may complain, the book has the virtue of explaining clearly basic principles and procedures.

All the chapters have been revised, most of them extensively. Rearrangement of the chapter contents to present material in the order of increasing complexity has been executed in the fourth edition. This change is consistent with the author's intention of presenting his subject to the resident or practicing ophthalmologist rather than to the specialist in plastic surgery. Three new chapters include a chapter on radiotherapy by Dr. Joseph Newall, and one chapter on chemosurgery-electrodesiccation by Dr. Perry Robins. These two chapters on controversial subjects conclude with surgical rebuttals by Dr. Fox which help to maintain a balanced perspective.

Purists may object to certain aspects of literary style and to the frequent (sometimes extensive) historical footnotes included in the text. Others will enjoy the casual style and historical commentary which together help to make this book much more readable than most surgical texts.

In summary, this book covers its intended subject clearly and thoroughly. It has no serious competitor as a single, concise and reliable source of basic information for the resident and general ophthalmic surgeon.

ROBERT S. HEPLER, M.D.

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RECONSTRUCTIVE SURGERY OF THE MIDDLE EAR—Adolph Wolf-erman, M.D., Attending Physician in Otolaryngology: Brooklyn Eye and Ear Hospital, Kings County Hospital, Brooklyn Jewish Hospital, New York Polyclinic Hospital, Brooklyn, and State University of New York (Downstate Medical Center). Illustrations by Lou Barlow. Grune & Stratton, Inc., 757 Third Avenue, New York, N.Y. (10017), 1970. 184 pages, \$25.00.

This easily readable, well thought out text is divided into several large categories—physiology, pathology, operative technique, pre- and postoperative care and complications with an interesting and timely final short paragraph on medico-legal implications. Despite its title of "Reconstructive Surgery of the Middle Ear," minimal time is given to reconstruction of the traumatically damaged ear, to the congenital ear, with the vast bulk of the text being devoted to reconstruction of the infection damaged ear or tympano-plastic surgery per se. Rather than being strictly a "how I do it" type text, Dr. Wolferman gives recognition to other methods of approach to the same problem in his completely thorough and low key presentation. Valuable as reference material and conservative in outlook, this publication can be put to great use by most otolaryngologists.

BERNARD M. KRAMER, M.D.



Tracheal Stenosis

D. FREDERICK KNUDSEN, M.D., and ROY COHN, M.D., *Stanford*

The increasing use of endotracheal intubation in support of various surgical methods has resulted in more injury to the tracheal mucous membrane than was formerly supposed. Tracheal injury may result in fibrosis and narrowing of the trachea. When tracheal stenosis is of a sufficient degree to necessitate repeated bronchoscopies and dilations, the patient's time under medical care and total morbidity may be considerably lessened by aggressive approach, involving resection of the diseased portion of the trachea.

TRACHEAL STENOSIS, as seen today, is largely a "disease of medical progress." With the advent of improved, more aggressive management of airway and pulmonary problems with various types of intubation devices has come a brand new complex of assorted problems. In the past, tracheal stenosis was an infrequently seen lesion associated with rare tumors, pulmonary tuberculosis, and the problem of extrinsic compression. As the philosophy of management of thoracic injuries changed, and as cardiac surgery came into its own, more and more patients were subjected to tracheal intubation. From among them has come a small but significant group of patients with tracheal injury secondary to intubation which has led to tracheal stenosis. Although intubation is the direct cause of the lesion, there are multiple factors connected with the intubation that contribute to the development of the lesion.

Much work¹⁻⁶ has been done to define predis-

posing factors in an attempt to improve management and reduce the incidence of strictures. Early conservatism in treatment has given way to an aggressive philosophy with a gratifying improvement in subsequent results. The purpose of this presentation is to describe three illustrative cases and to review the current etiologic concepts and management, as well as the results of treatment of this lesion.

Case 1. A 33-year-old white man was admitted to the Santa Clara Valley Medical Center emergency room on 5 April 1969 with a nine-hour history of severe substernal chest pain radiating to both arms, associated with nausea and diaphoresis. The patient's father had died at age 41 of a myocardial infarct, as had one uncle, also at age 41. Cardiac arrest occurred while the patient was in the emergency room, requiring defibrillation, external cardiac massage, and tracheal intubation. An electrocardiogram confirmed an acute myocardial infarction. Following successful resuscitation from the arrest, the patient was comatose, unresponsive and had no spontaneous respirations. On 6 April, elective trache-

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Submitted, revised, November 4, 1970.

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ostomy was carried out under local anesthesia in the operating room. The tracheal incision extended from the second to the fourth tracheal rings. A No. 9 tracheostomy tube was inserted without difficulty. The patient made a slow recovery from cardiac arrest, with a stormy course complicated by pneumonitis and seizure activity. The patient required assisted respiration until 19 April, after which spontaneous respirations were adequate. The tracheostomy tube was removed 9 May 1969 after 35 days of tracheal intubation. Cultures from serial tracheal aspirates revealed a hemophilus species, alpha and beta streptococcus, candida albicans, bacterioides, diphtheroids, neisseria, and E. coli. Following removal of the tracheostomy tube, the patient was transferred to the Rehabilitation Service for management of cerebral impairment. He made slow and incomplete recovery from the anoxic insult but improved enough for transfer to a nursing home. There he did well until 30 August 1969 when progressive shortness of breath developed, with wheezing. Transferred to the emergency room on 31 August 1969, he was treated for a bronchospasm without relief of symptoms. An x-ray film of the chest showed tracheal stenosis. While in the emergency room, the patient's condition deteriorated rapidly, and attempts at oral and nasal intubation of the trachea were unsuccessful. Tracheostomy was performed in the emergency room and tight stenosis was encountered at the cuff site. This was dilated bluntly with a clamp until a 6.5 mm uncuffed tube could be passed. Respiratory distress was immediately relieved. Over the next 72 hours, the stricture dilated rapidly and required progressively larger tubes for occlusion of the airway around the tube.

At subsequent bronchoscopic examination some mucosal ulceration, but no persisting stricture was observed. The tracheal tube was removed and the skin allowed to close. Tomography on 30 September 1969 showed no recurrence of stenosis. The patient did well until 13 October 1969 when shortness of breath again prompted an emergency room visit, and he was handled with symptomatic therapy. He returned the next day with continuing complaints of shortness of breath, and a tracheogram at this time revealed recurrence of the stricture.

Tracheostomy was again performed, this time in the operating room, and the stricture dilated. After appropriate preparation, the patient was

taken to the operating room on 24 October 1969 and underwent a tracheal resection with a primary anastomosis via a median sternotomy incision. His postoperative course was uneventful, and the tracheostomy tube was not re-inserted at the conclusion of the procedure. Six weeks later bronchoscopic examination was repeated, and satisfactory healing of the suture line, with no recurrence of stricture, was noted.

Current follow-up at one year postoperatively reveals no recurrence of the stricture, and the patient has had no further respiratory difficulties. However, his mental state continues to be suboptimal.

Case 2. The patient, a 42-year-old woman, was admitted for the first time 6 May 1970 with chief complaint of tracheal stenosis. She had been in a state of good health until January 1970, when she took a massive overdose of glutethimide (Doriden) and was treated at another hospital. She was comatose for two weeks and tracheostomy and assistance with respiration were necessary. After recovery she was found to have tracheal stenosis at the level of the sternal notch. Tracheostomy was done again, just below the stenotic area, at another hospital in March 1970. Over the following two months she had tracheal dilation four times with passage of an 8 mm bronchoscope, which consistently showed narrowing down to 3 or 4 mm. A post-dilatation tracheogram showed a 1.5 cm segment of stenosis just above the sternal notch and just below the area of the last tracheostomy. Even with the tracheostomy tube in place, the patient complained of shortness of breath and wheezing, which worsened with activity and talking. She did her own tracheal care at home, where she lives with her husband and a six-year-old daughter. She was referred for definitive treatment. She appeared in no acute distress at the time of admittance. Blood pressure was 105/75 mm of mercury and respirations were 22 per minute and slightly labored. A tracheotomy tube was in place. Head and neck examination were within normal limits except for the tracheostomy. Breath sounds were clear on both sides of the chest. The breasts were normal. Heart rate and rhythm were normal and there were no murmurs. The abdomen was soft and without masses or tenderness. Rectal-pelvic examinations and the remainder of the physical examination were within normal limits. The impression was tracheal sten-

osis secondary to tracheostomy tube after an overdose of Doriden. X-ray studies of soft tissues of the neck did not reveal the area of stenosis, which was believed to be at the sternal notch. No abnormality was noted on an x-ray film of the chest. An electrocardiogram was normal. Complete blood count was within normal limits. The hematocrit was 43. Urinalysis was normal. Chemistry screening battery was within normal limits, as were electrolytes. On 7 May 1970 the tracheostomy tube was removed without immediate difficulty to the patient but within three hours she was having increasing respiratory difficulty with retraction, and the tracheostomy tube was replaced. On 11 May resection of the trachea at the site of the stoma and stenosis was carried out. Bronchoscopy showed only a 1 to 2 mm opening above the tracheostomy tube. Postoperatively the nasal endotracheal tube was kept in place for two days and then removed. The patient did well and the wound healed nicely. On 16 May 1970 she was discharged. Her talking and breathing were within normal limits at this time. Four months later the patient was well.

Case 3. The patient, a 19-year-old boy, was readmitted to the Stanford Medical Center 31 January 1970, after having been discharged three days earlier with a diagnosis of upper respiratory obstruction. A long endotracheal tube had been used four weeks earlier in treatment for drug ingestion, and tracheal stenosis had developed. The patient had first been admitted 21 January 1970, and bronchoscopy then had shown the stenosis. The area was reamed and a tracheal stent inserted. When the patient was readmitted because of re-obstruction, the T tube was found to be plugged with secretions. On 5 February he was taken to the operating room, and when bronchoscopy showed re-stenosis of the area, another 12 mm tracheal stent was inserted. On 13 February the patient was sent home, where he had a suction apparatus to take care of the stent. Nevertheless, he had increasing trouble with secretions and blocking of the upper airway. He was readmitted 24 February 1970, with complaint of difficulty in breathing, for definitive treatment of the tracheostenosis. Tomograms of the trachea showed stenosis for approximately 3 to 3.5 cm above the stoma of the tracheostomy. On 28 February indirect laryngoscopy was carried out. Granulation tissue, completely occluding the trachea in the sub-glottic region, was seen. The

tube was not seen. On 9 March four rings of the trachea (approximately 5 cm) was resected. The postoperative course was ordinary. The patient's neck was kept in a flexed position with the chin down. Cloxacillin was administered until 16 March and the patient remained afebrile. Postoperative x-ray films of soft tissues of the neck showed full diameter at the site of tracheal anastomosis. The patient was discharged 30 March and at last report was working and had no difficulty in breathing.

Etiology

The etiology of tracheal stenosis can be divided into several broad categories. Tracheal intubation, external trauma, tumors, and tracheomalacia are the most important sources of damage to the trachea. Tracheomalacia is usually due to extrinsic compression seen with large goiters, (particularly the substernal type), to congenital vascular rings, and to other mediastinal tumors that produce prolonged direct pressure on the trachea. The tracheomalacia with expiratory collapse seen in the patient with chronic obstructive pulmonary disease is a cause of a different kind, and the methods of treatment are considerably different.

Intrinsic tumors of the trachea are quite rare but can produce a clinical syndrome indistinguishable from a stenotic scar. The prototype tumor is a cylindroma of the trachea which probably is a low grade adenocarcinoma. Some 20 histologic types of tumor have been described, but there are basically four main categories. These present a wide spectrum of degree of malignancy, but many of these are low grade and lend themselves well to local resection for cure.

External trauma to the trachea in the form of blunt or penetrating injury can lead to stenotic lesions that require subsequent therapy. Chemical injuries such as may be caused by smoke inhalation, aspiration of gastric contents, or aspiration of ingested caustic solutions have not been described as a cause of localized tracheal stenosis, although severe diffuse superficial injury may occur. The use of tracheal intubation is the most common, most preventable cause and the lesion produced is probably the most easily treatable. The use of tubes in the trachea can cause damage regardless of the site of entry—nasal tracheal,

oral tracheal, or tracheostomy. Stenosis may follow intubation for even so short a time as 36 hours, but usually it is associated with longer periods.

Infection in the airway is another prominent contributing factor. In spite of fastidious local care and constant reminders to the nursing staff about the necessity for sterile technique, in virtually all cases cultures of material taken from a tracheostomy wound grow infective organisms. The patients are often receiving antibiotics that eliminate the local flora and permit the appearance of an antibiotic-resistant opportunistic invaders. In a specially designed and carefully run respiratory care unit, Gibson⁶ reported 154 consecutive patients requiring respiratory support. One hundred and seven had cultures, of which only 12 were sterile. The most common organisms cultured were *E. coli*, Friedlander's bacillus, staphylococcus, pseudomonas, and candida albicans. Of 96 survivors, ten had ulcerated lesions of the trachea with positive cultures in the tracheal aspirate. Clinically significant tracheal stenosis developed in all ten of these patients.

Physical characteristics of the tracheostomy tubes also play a role in the development of tracheal lesions. Excessively large tubes, high pressure in the tube cuff, and the chemical composition of the tube are all potential sources of trouble. It is clear that high cuff pressures will produce a local ischemic lesion in the relatively rigid trachea, leading to ulceration of the trachea, with erosion and subsequent destruction of the cartilagenous support. Specially designed low pressure cuffs with broad bearing on the tracheal wall produce essentially no damage to the respiratory epithelium even with prolonged constant cuff inflation. Portex endotracheal tubes used to contain an irritative chemical that sometimes produced stenotic lesions with both tracheal and urethral intubation. The composition of these tubes has since been changed, and since then no such lesions have been ascribed to them.

Diagnosis

The diagnosis of tracheal stenosis is relatively simple if the possibility is considered, as it should be if there is history of tracheostomy or prolonged nasal tracheal intubation. The only major difficulty is that patients remain asymptomatic, with no physical signs, during the early phases of

tracheal narrowing. But when the stricture reaches a critical stage symptoms may become acute shortness of breath, inability to clear secretions, even sudden death. History, other than that of previous tracheal intubation, is generally not helpful. Wheezing may be heard in the central portion of the chest or in the neck. This may occur only on expiration or with forced expiration. Probably every significant stricture will have some audible wheeze in the neck. Posterior-anterior and lateral x-ray films of the neck with soft tissue technique will generally show the narrowed air column with good detail. Contrast studies with tantalum powder or aqueous lipiodal will give further information. Bronchoscopy will reveal the lesion without difficulty, but with monocular vision it is difficult to determine how long a segment is damaged. Bronchoscopy is primarily indicated to evaluate the status of the remainder of the tracheobronchial tree and to assess the pliability of the strictured area. Even though the bronchoscope may easily pass through the stricture, if the procedure is done under local anesthesia, forced expiration or cough will reveal so decided a narrowing of the lumen that the airway is inadequate.

The dilating effect of bronchoscopy may produce temporary relief of the airway obstruction, but this is generally short-lived, and the improvement should not lull the physician into a false sense of security. Serial bronchoscopy for dilatation or prolonged close follow-up is necessary in the management of these patients.

Treatment

As with many other problems, this lesion is better prevented than treated. Many ingenious tracheostomy tubes have been devised with this in mind. Tubes with oversized cuffs designed to produce a more diffuse and lower pressure on the tracheal wall have been used. The disadvantage of these tubes is that the redundant cuff can slip over the end of the tube and close it completely. Devices that trigger cuff inflation by the respirator so that balance is maintained between the pressure in the cuff and in the airway have been used. Since the cuff deflates cyclically during expiration, it presses only intermittently on the tracheal wall. This has theoretical appeal, but it eliminates the protection of the inflated cuff against aspiration of swallowed or vomited ma-

terial. In addition the mechanisms are complex and mechanical failures sometimes occur.

As was mentioned earlier, bronchoscopy can give temporary relief of symptoms, and some patients can be successfully managed over long periods by repeated bronchoscopy, but this requires close cooperation by the patient, close observation, and elasticity at the point of stricture.

Internal stenting with reinforced silastic T-tube stents has been used at Stanford Hospital with moderate success. These tubes are placed in the trachea following dilation of the stricture with the right-angle portion extending through the tracheostomy stoma. These can be used for stoma or cuff level strictures. The tubes are generally left in place for nine months and then removed. They require close early supervision, as secretions may become a problem. With long-term use, secretions become less troublesome. However, exuberant granulation tissue stimulated by the presence of a foreign body can lead to narrowing of the trachea or occlusion of the tube. Another hazard is displacement of the tube, with occlusion of the airway ensuing. Some patients tolerate the tubes well and retain them in appropriate positions to a successful conclusion of their stenosis problem. Others have major local problems which require termination of this form of treatment.

Surgical resection of the stenotic lesion is the treatment of choice for localized fibrous strictures if the narrowed segment cannot be dilated easily or stent insertion is poorly tolerated by the patient. Short areas of trachea can be resected and primary repair done with relative ease. The surgical approach may be from the neck, the mediastinum or the right side of the chest, depending upon the position and length of the stricture. Thus far, prosthetic replacement has been uniformly successful. Synthetic material does not produce an adequate functioning trachea in that secretions are poorly mobilized, and healing between the prosthesis and the trachea generally fails. The only limiting factor in resection of the trachea is the length of the lesion. It is important to carry the resection back to normal trachea, above and below, for good results without recurrence.

Grillo,⁷⁻¹¹ in extensive studies to determine the maximum length of trachea that can be resected with primary repair, demonstrated that tracheal

anastomosis with greater than 1700 grams of tension will separate or will heal by scarring that makes a new stenotic lesion. Various maneuvers can be used to obtain length to facilitate a tension-free anastomosis. The average length as determined by cadaver studies is 11 cm. "Lowering the trachea" by release of the suprathyroid attachments as described by Dedo and Fishman³ (2 to 3.5 cm); flexion of the neck (4 to 5 cm); mobilization of the right hilum with division of the pulmonary ligament (3.5 to 5 cm); division of the left mainstem bronchus with reinsertion into the bronchus intermedius; freeing the pulmonary vessels from the pericardium; and advancement of the cervical trachea on a vascular pedicle from the inferior thyroid artery (4 cm) have all been described. These methods need be used only for relatively long strictures or when the mediastinum must be avoided for some reason, such as previous cardiac operation. In the usual short stricture, local mobilization of the strictured area of the trachea combined with flexion of the neck is all that is required for adequate length to permit tension-free anastomosis.

Results

In general, in the very small series reported the best results are with primary repair. Only Grillo's series is big enough to warrant conclusions. Use of a T-tube stent is not widely reported, and results at Stanford have not yet been published. No one has described a case using a combination of laryngeal lowering and extensive intrathoracic mobilization in the same patient. Only four cases of the laryngeal lowering have been reported, and in all of them the patients are doing well. Combining six published series, the following results were compiled:

Procedure	No. of Patients	Results			Deaths
		Good	Satisfactory	Poor	
Dilation	13	4	7	2	0
Resection	44	32	5	7	3

Undoubtedly many cases successfully treated by dilation alone have not been reported. It is probable that a higher proportion of operative cases are reported, for the literature is still so scant that reports are acceptable for publication. Therefore it is a reasonable assumption that the results listed above may be considerably biased

and that they do not reflect the true picture. At the Santa Clara Valley Medical Center in the past ten years there have been seven patients with established diagnosis of tracheal stenosis. Five were managed with endoscopic removal of granulation tissue or dilatation, one by permanent tracheostomy, and one by resection (presented herein). All these patients are doing well, although two of them have been lost to follow-up.

Conclusions

Tracheal stenosis is an uncommon lesion largely occurring secondary to tracheal intubation with respiratory support. Contributing factors are multiple, but the final common pathway is a localized destruction of tracheal wall with subsequent healing by fibrosis that causes a stenotic lesion as contracture occurs. There are several well-established means of treatment, with results generally satisfactory if the diagnosis is established early and the patient is followed carefully to the conclusion of the treatment. Studies being conducted in prevention of the lesion will probably render the presently used operative

treatment relatively obsolete. Prophylaxis is simple in concept, applying the concept is extremely difficult and requires close cooperation between physician and nursing staff.

TRADE AND GENERIC NAMES OF DRUGS

Doriden®glutethimide

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BIOPSY BEFORE RADICAL TREATMENT—USEFUL AS A GUIDE TO BREAST CANCER THERAPY

"In the search for better methods of managing early breast cancer, we have found a higher survival rate in 589 women who had an excisional biopsy a short interval before radical treatment. Certainly this method of management . . . is a simple and safe addition to the presently accepted methods of treatment. For one thing it means that the patient does not have to cope with two shocks at the same time—first, the realization that she has breast cancer and second, the unpleasantness of the major procedure. . . .

"The results suggest that a simple excision of the breast lump would prove to be a useful clinical method of sorting out patients with a favorable prospect. The period of delay could be used to advantage for clinical and histological assessment to provide a better prognostic index for each individual patient. Certainly the prevalent concept that a previous excision is a hazard to survival in breast cancer becomes a myth. After the primary breast lump which proves to be carcinoma has been removed, there is a much larger choice of major therapy."

—M. VERA PETERS, M.D., Toronto
Extracted from *Audio-Digest Surgery*, Vol. 16, No. 24, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057

Complications of Smallpox Vaccination, 1968

Results of a Statewide Survey in Alaska

PAUL S. CLARK, M.D., Anchorage, Alaska, AND
J. MICHAEL LANE, M.D., Atlanta

■ *A survey was made to determine the incidence in Alaska of complications of smallpox vaccination during 1968. Of the 206 medical personnel responding to the questionnaire, 20 (or 9.7 percent) observed a complication. Twenty-six complications were reported, 20 of which occurred in primary vaccinees. Accidental implantation was the most common complication, but two cases of eczema vaccinatum and two of generalized vaccinia were observed. There were no deaths or cases of postvaccinial encephalitis or vaccinia necrosum. Of the 26 complications, 19 were theoretically preventable.*

THE EFFICACY OF SMALLPOX VACCINATION, the first immunizing procedure ever used in medicine, is beyond question. Smallpox has been eradicated from the United States and Canada, and Europe is essentially free from the disease aside from occasional importations from remaining endemic areas in Africa and Asia. Only recently have sound data been assembled concerning the incidence of complications of vaccination within the United States. In 1963, two surveys were conducted. One focused on the more severe complications, assembling national morbidity and mortality data from persons who had received

vaccinia immune globulin (vig), from death certificates, and from state epidemiologists.¹ The second was a retrospective survey of 4,900 physicians in four states whose combined population was 4.8 percent of the total for the United States.² The limitations of data biased toward the more severe complications and of data collected by retrospective surveys led the authors to conclude that their statistics on the frequency of complications must be viewed as estimates.

During 1968, a prospective survey of medical personnel in ten states, including Alaska, was conducted to obtain more precise information on the incidence of smallpox vaccination complications. In Alaska, 75 percent of the smallpox vaccine is distributed through three regional public health laboratories. An accurate estimate of the number of vaccinees can therefore be obtained.

From the Epidemic Intelligence Service (Dr. Clark) and the Smallpox Eradication Program (Dr. Lane), Center for Disease Control, Health Services and Mental Health Administration, Public Health Service, United States Department of Health, Education, and Welfare, Atlanta, Georgia.

Submitted November 30, 1970.

Reprint requests to: Alaska Activities, Ecological Investigations Program, CDC, 225 Eagle Street, Anchorage, Alaska, 99501 (Dr. P. S. Clark).

Materials and Methods

In January 1968, 107 private physicians who were specializing in pediatrics, internal medicine, general practice and dermatology in Alaska received an introductory letter explaining our interest in determining the incidence of complications of smallpox vaccination during calendar year 1968. A brief description of the types of complications was included and a stamped, self-addressed, postcard reporting form was supplied. A similar letter was sent to 65 Public Health Service physicians and 62 public health nurses. In January 1969, these persons were contacted again

and asked whether or not they had seen any vaccination complications. If they had, they were contacted by mail or phone for detailed clinical information. Each patient was identified by name; four duplicate reports were identified. Information was also received from the National Communicable Disease Center on one patient treated with vaccinia immune globulin.

We estimated the total number of vaccinees by calculating the number of doses distributed by the three regional laboratories and estimating that private physicians administered no more than 25 percent of this total. Approximately 29,000 persons were vaccinated in Alaska in 1968.

TABLE 1.—COMPLICATIONS OF SMALLPOX VACCINATION—Response to Questionnaire by Physicians and Nurses Alaska 1968

	Number surveyed	Number of replies	Percent responding to questionnaire	Number reporting at least one complication
Private physicians	107	93	87	8
Public Health Service physicians	65	56	86	5
Public health nurses	62	57	92	7
Total	234	206	88	20

Results

Of the 234 physicians and nurses contacted, 206 (88 percent) responded to the survey (Table 1). Of those responding, 20 (9.7 percent) reported at least one complication.

The complications reported are presented by age, diagnosis, and vaccination status in Table 2. Clinical information was obtained on all 26 cases. Most of the reported complications were found to be compatible with the original diagnosis, but three cases of vaccinia necrosum were reclassified as severe primary reactions because no underlying immunological disease was associated with this

TABLE 2.—COMPLICATIONS OF SMALLPOX VACCINATION—Distribution of cases by age diagnosis and vaccination status

Age in years	Accidental vaccinia implantation	Severe local reaction*	Bacterial infection at site of vaccination	Generalized vaccinia	Eczema vaccinatum	Arthritis	Total
Primary vaccinees							
<1	2	1					3
1-4	6	2*	3	1	1	1	14
5-9	1						1
10-19	1				1		2
20+							0
Sub-total	10	3	3	1	2	1	20
Revaccinees							
<1							0
1-4		1					1
5-9	1			1			2
10-19	1						1
20+	1	1					2
Sub-total	3	2	0	1	0	0	6
TOTAL	13	5	3	2	2	1	26

*Including one case of bullous erythema multiforme.

condition and the patients recovered without specific therapy.

Accidental implantation of the vaccinia virus was the most common complication and is defined as implantation of the virus in the eyes, mouth or other parts of the body in a person without eczema or other preexisting skin lesion.² Of the 13 patients reported, ten were primary vaccinees. The illness was mild in each case; no one was put into hospital or received *vic*, and all recovered spontaneously either with or without symptomatic therapy.

Severe local reactions were observed in five persons, and in four they cleared spontaneously in one to three weeks. In the fifth, erythema multiforme developed. This is the most common nonspecific dermatologic eruption following vaccination.³ The patient was a boy two and a half years old, a primary vaccinee. Following a severe primary reaction, bullous lesions spread from the vaccination site. Recovery occurred within seven days indicating that he had a benign form of this disease and that treatment with corticosteroids and antibiotics may not have been necessary.

Three cases of bacterial infection were reported in infant primary vaccinees. Gradual recovery was associated with antibiotic therapy and symptomatic treatment.

Generalized vaccinia is defined as the development of generalized vaccinal lesions in the absence of eczema or other preexisting skin lesion.² Two patients had mild generalized vaccinia characterized by a papulovesicular eruption of not more than 50 lesions. Neither was admitted to hospital or treated with *vic*.

Eczema vaccinatum may be similar to generalized vaccinia but occurs in a person with eczema or a history of eczema.² Two cases occurred. This complication developed in a 15-month-old primary vaccinee seven days after vaccination. After treatment with 5 ml of *vic*, she recovered within three days. The other case occurred in an 11-year-old girl, a revaccinee, with eczema on her legs. The generalized eruption cleared spontaneously in seven to ten days.

In one patient monarticular arthritis developed, possibly secondary to vaccination. Axillary adenopathy, limitation of movement, swelling and local heat in the elbow distal to the eschar occurred in a one-year-old Eskimo girl 14 days after vaccination. There was no evidence of bone destruction or osteomyelitis on roentgenographic examination,

and no fluid was obtained from the arthrocentesis. Other investigators have succeeded in isolating vaccinia virus from the synovial fluid in a patient with monarticular arthritis following vaccination,⁴ and patients with polyarticular arthritis with ecchymoses or petechiae have recently been reported.^{5,6}

The most severe reactions to vaccination, vaccinia necrosum and postvaccinal encephalitis, were not observed in Alaska in 1968. Vaccinia necrosum, or progressive vaccinia, is defined as spreading necrosis at the site of vaccination with or without metastatic necrotic lesions.² It occurs in persons who are immunologically incompetent, especially (but not restricted to) those with Hodgkin's disease, leukemia, athymia, systemic lupus erythematosus, and agammaglobulinemia. Vaccinia necrosum may also develop in persons receiving immunosuppressive therapy.

During 1968 approximately 29,000 persons were vaccinated in Alaska. Hence the complication rate for that year was 0.89 per 1000 vaccinations. Twenty of the 26 complications occurred in primary vaccinees. What proportion of the total was made up of primary vaccinations is not known but the complication rate is probably much higher for primary vaccinees.

Discussion

The nationwide survey of smallpox vaccination complications in 1968 was designed to obtain a more accurate appraisal of the risks of vaccination and to further delineate the incidence of the life-threatening complications—vaccinia necrosum, postvaccinal encephalitis and eczema vaccinatum.

The advantages of a prospective survey were clearly apparent in Alaska. Accurate historical information was obtained from nearly every patient. The initial diagnosis was usually correct, and only cases that occurred in 1968 were reported. In the surveys of 1963 complications, which were carried out in 1965, similar accuracy of diagnosis was not obtained, and many of the reported complications had occurred before 1963.²

Certain limitations are also apparent in this study. Although physicians and nurses were notified of our interest in vaccination complications at the beginning of the study, only four of the 26 complications were reported by postcard. As there was a 12-month interval between the first letter and the last, a few complications may not have

been detected. The interval between the occurrence of the complication and the case investigation may have obscured some details or led to reporting complications not casually related to vaccination.

The overall complication rate of 0.89 per 1000 is comparable to the 1963 figure of 0.65 per 1000 vaccinees per year.² The higher rate reported for Alaska may be a reflection of the vigilance resulting from the introductory letter. Cases of postvaccinal encephalitis and vaccinia necrosum were not reported in Alaska. These complications occur at rates of respectively, approximately two and one per million primary vaccinations.¹

Seven of the Alaska complications were theoretically not preventable. The three cases of bacterial infection, two cases of generalized vaccinia, one case of erythema multiforme and the probable case of arthritis were not associated with poor vaccination technique or contraindications to vaccination and could not have been predicted or prevented. Some of the 13 cases of autoinoculation might have been avoided by carefully remov-

ing residual droplets of vaccine from the vaccination site. The four cases of severe local reaction could perhaps be secondary to excessively vigorous technique. The two cases of eczema vaccinatum could have been eliminated by screening vaccine recipients more carefully.

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TONGUE CANCER—IRRADIATE OR OPERATE?

"In experienced hands, cancer of the oral tongue and floor of the mouth can be managed well by either radiation or surgery. However, there may be some factors other than experience which dictate one or the other methods of management. For example, the elderly patient ordinarily tolerates a short surgical treatment better than a prolonged course of radiation therapy. The exophytic cancer will ordinarily respond well to irradiation therapy whereas the deeply infiltrating cancer and one which is attached to or invades bone may be better treated surgically. Cancers associated with leukoplakia can usually be better treated by surgery than by irradiation since the leukoplakia can be managed at the same time by resection and skin graft. A similar situation applies to the patient with multiple primary cancers of the oral cavity. Surgical treatment is to be preferred. The mental status of the patient may also dictate a surgical treatment, for the mentally disturbed and uncooperative patient is not likely to tolerate either prolonged irradiation or a radium implant. The chronic alcoholic and the heavy smoker may be better treated by surgery for two reasons: (1) the incidence of multiple mucosal abnormalities seems to be much higher in these patients, and (2) irradiated mucous membranes tolerate poorly the insults of excessive smoking."

—ALONDO J. BALLANTYNE, M.D., Houston
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Personality Factors Associated with Frequency of Marijuana Use

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■ A number of personality and style-of-life variables were found to be significantly related to frequency of marijuana use, in a study of 1215 students on the University of California, Los Angeles, campus. Compared with the non-user, in composite the typical marijuana-user is somewhat depressed, more inclined to doubt his emotional adjustment. He likes to take risks and seeks stimulation; he has strong political opinions; he believes in punishment for law-breakers, but he is more likely to question it. He is not religious; he is less well identified with parents, and he has a lower opinion of their marital adjustment. He is not decisive about career goals; he is a fine arts or liberal arts major. He uses alcohol, sometimes in combination with marijuana; he first tried marijuana after entering college and is not increasing his use. The typical marijuana-user in the sample uses it infrequently, twice a month or less often, and is not likely to be using other drugs. The frequent user probably uses other drugs.

THE USE OF MARIJUANA on college campuses is both widespread and increasing. Chronic users have been described as developing "passive, inward-turning, amotivational characteristics,"^{1,2} but there has been little research directed toward personality differences between users and non-users.

Just recently Robbins et al³ in a survey of medicinal and drug use patterns at two colleges found that students who use drugs described themselves as being moody and unhappy significantly more often than did non-users. Hinckley and his co-workers⁴ reported similar findings.

In a previous study⁵ of a fairly homogeneous group of freshmen and sophomores taking basic psychology, we found more frequent use of marijuana to be associated with "seeking stimulation,"

"psychopathic deviancy," "independence of judgment about obeying laws," and "admitted existence of long-standing emotional problems."

The present study is an extension of that preliminary investigation to a larger, more heterogeneous, and more representative sample of University of California, Los Angeles, students to obtain more information on marijuana use patterns as well as on associated personality variables.

Methods

An anonymous questionnaire and a psychological inventory form were given to students applying for medical (non-psychiatric) treatment at the UCLA Student Health Service. When each student registered at the information desk, he was given the packet of materials and a letter asking for his cooperation and assuring his anonymity. He was asked to return the materials if he did not wish to complete them or did not have time to do so. After a number of completed sets were returned by mail, the investigators also enclosed an addressed envelope for those subjects who wished to complete the tests at home, but no pressure

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TABLE 1.—*Marijuana Use in Sample of Students*

<i>Marijuana Frequency</i>	<i>Use Marijuana*</i>	<i>Increasing Use**</i>	<i>Decreasing Use</i>	<i>Used Other Drugs**</i>	<i>Still Use Other Drugs**</i>
Never tried	47.5			3.7	1.5
Tried and quit	16.9			22.4	3.3
Less than ½ X month	11.7	1.5	60.4	42.0	10.0
½ X month	9.4	2.6	41.6	43.8	17.5
½ X week	9.6	6.8	30.8	70.9	43.6
Almost daily	4.9	18.3	10.0	95.0	71.7

*Percentage of all subjects

**Percentages of subjects in each of the six marijuana categories

was put on them to do so. Of 1250 sets of material distributed, 1215 were returned.

The sample of 1215 consists of 50 percent males and 50 percent females with average age 21 years. Twelve percent are freshmen, 15 percent sophomores, 22 percent juniors, 25 percent seniors, and 26 percent graduate or other special students. Almost all have chosen majors, 49 percent in some liberal arts field. Only 18 percent have not yet decided on a career. Slightly over half (56 percent) live on or near campus; 55 percent live alone or with a roommate, 30 percent live with their families, and 15 percent live in some other group setting. Most (83 percent) are single, 15 percent married, 2 percent formerly married. Less than 1 percent have had any military service.

The sample compares well with the UCLA campus as a whole with respect to age and sex distributions, but it is somewhat low on freshmen. Data on the other variables for the entire campus were not available for comparison.

The questionnaire consists of items providing descriptive data, rating of parental adjustment and role of religion, and items relating to use of marijuana, alcohol and other drugs. The psychological inventory consists of four scales (Psychopathic deviate (pd), Depression (d30), Taylor Manifest Anxiety (mas), Barron Ego Strength (es)) derived from the Minnesota Multiphasic Personality (MMPI) Inventory,⁶ a risk-taking propensity scale,⁷ a stimulus-seeking scale,⁸ and nine items relating to various personality variables specially constructed for the study. The questionnaire and inventory yielded data on such personality variables as ego strength, emotional adjustment, goal-orientation, rebelliousness, etc.

Data were analyzed by means of chi square tests and Pearson product moment correlations.

The sample was divided into six sub-groups according to reported frequency of use of marijuana: those subjects who have never tried it, those who have tried it without continuing its use, those who report using it less often than once a month, once or twice a month, once or twice a week, and almost daily. Thus there were two control groups of non-users and four groups of marijuana-users for chi square tests. For computing correlation coefficients each subject was assigned a score representing his own frequency of use.

To simplify presentation, the exact values of statistical tests are not given. Each result reported is significant at better than the .001 level of probability. This stringent requirement was made because of the large number of tests computed and the large size of the sample.

Results*

Marijuana use patterns. As Table 1 indicates, about half of the subjects (ss) have tried marijuana (MJ) but only 35.6 percent continue its use; 4.9 percent using MJ almost daily, 9.6 percent once or twice a week, 9.4 percent once or twice a month, and 11.7 percent less often than once a month. Of those who use MJ, 77.9 percent first started after entering college, with daily users more likely than others to have first tried MJ before college. Of those who are using MJ only a small number (5.6 percent) are increasing their use of it as time goes on; most (54.1 percent) are using at about the same level, and a sizable fraction (40.3 percent) are actually decreasing in frequency of use.

Thus the typical (or, more correctly, modal) MJ user on campus first tried MJ after entering

*Results are based on data collected in the fall of 1969. More recent studies have indicated increased use of drugs.

college; he indulges once or twice a month or less often; he is not increasing his use.

Psychological variables. Both non-users score within the normal range on the four MMPI scales and within the range usually obtained with normals on the Risk-Taking Propensity and Stimulus-Seeking Scale. Within the framework of normality, more frequent MJ use is associated with greater depression, more propensity for taking risks, and somewhat greater need to seek stimulation. In contrast both to clinical expectations and to the findings in our earlier pilot study, there was no tendency for MJ users to have elevated *pd* (Psychopathic Deviate) scores.

We found no great degree of alienation from parents in this sample. Roughly two-thirds of all ss responded "false" to "I just can't see things the way my parents do," and "My parents don't make much effort to understand my point of view"; however, MJ users do appear to be somewhat more alienated than do non-users. (Here the difference is between users and non-users, not a linear relationship between responses and frequency of MJ use). Most ss rated their parents as getting along "very well" together, and only 5.6 percent said they were not getting along well. The more frequent the use of MJ, the lower was the rating of parental accord.

Only a quarter of ss agree that "A person should not be punished for breaking a law he thinks is unreasonable." Here is an outstanding difference in response pattern: 16.1 percent of ss who have never tried MJ respond "true," and the proportions climb steadily to 54.5 percent for daily MJ users. (It will be noted, however, that almost half who almost daily break the law by using MJ do not feel they should escape punishment).

Almost as pronounced was the difference in response to "I have strong political opinions." Over half do (61.5 percent). Ss who have never tried MJ are less likely (43.5 percent) to have strong opinions, and there is a tendency for more "true" responses to be associated with greater use of MJ.

The common impression that marijuana users are emotionally disturbed was not confirmed in this study of UCLA students. As noted before, MMPI indicators place this sample within the normal range on the variables studied. Rating their own adjustment, ss overwhelmingly claim good adjustment on the items "I am about as

well adjusted as most people" (86.4 percent true), "As long as I can remember, I have had more emotional problems than other people" (86.7 percent false), and "I have never had a really close friend" (91.7 percent false). On the "well-adjusted" item, daily MJ users were more likely to answer "false," but even here 76.4 percent responded "true." On the other two adjustment items, responses were distributed randomly.

There is a significant but low relationship between MJ frequency and "true" responses to "Sometimes I like to do something risky just for the fun of it," a finding consistent with the correlation of the risk-taking propensity scale. More than half (62.8 percent) of all ss do like to do something risky, frequent MJ users more so than infrequent or non-users.

As indicated in the description of ss, most of these students are goal-oriented, in that they have decided on majors and on careers. Even so, there are definite relationships with frequency of MJ use: the proportion of ss who have decided on careers decreases steadily from 63.6 percent for ss who have never tried MJ to 44.8 percent for ss who use it almost daily; fine arts majors are more likely than others to be frequent MJ users, as are liberal arts majors but to a lesser degree; whereas science and engineering majors tend to use MJ less frequently than the others. When the question is put in a more philosophical and less specific way, more than 70 percent answer "false" to "I don't really know what I want out of life," and there is no relationship with MJ use.

A relatively small fraction of ss (14.6 percent) say religion plays a great part in their lives; these ss are more likely not to have tried MJ, but there is no apparent relationship with frequency of use. Almost half (45.5 percent) of ss say religion plays little or no part in their lives, and 39.9 percent, some part. Here there is a clear relationship: 67.8 percent of daily MJ users say religion plays little or no part; the proportion decreases consistently to 31.5 percent of ss who have never tried MJ. The percentage ladder is reversed for ss who say religion plays some part in their lives, from 20.3 percent of daily MJ users to 47.8 percent of non-users.

To summarize the results on psychological variables: The typical (average) MJ user, compared with the non-user, is a little depressed. He likes to take risks and seeks stimulation rather than avoid-

ing it. He has strong political opinions. He does not really challenge punishment for laws considered unreasonable, but he is more likely to question them. He is less identified with his parents, and he has a lower opinion of their mutual adjustment. He considers himself emotionally well-adjusted, but he is more inclined to doubt the caliber of his adjustment.

This picture of the MJ user is consistent with but more detailed than that derived from our small pilot study, except for the notable absence of a relationship between PD score and MJ use that had been found before. The pilot study sample consisted of young freshmen and sophomore psychology students, as against this larger, heterogeneous and older sample—a difference which may have produced the discrepancy. One may speculate that the younger MJ user is more likely to use MJ in protest and rebelliousness.

Alcohol and other drugs. More ss report using alcohol (71.2 percent) than MJ (35.6 percent), and 25.8 percent use both. Of the latter, a surprising 70.7 percent use MJ and alcohol together, at least occasionally; in this group, one is no substitute for the other. The daily MJ user is more likely to use both at once, as would be expected, but even the very infrequent user does so from time to time.

In the total sample, 24.8 percent of ss have used other drugs such as hallucinogens, amphetamines, barbiturates, heroin etc., and half of these continue to use them. The decided relationship between frequency of use of MJ and use of other drugs, shown in Table 1, is the most highly significant relationship found in the study. The more frequently MJ is used, the more likely is the subject to have used other drugs. It may be seen in the table that only 3.7 percent of ss who have never tried MJ have tried any other drugs, compared with 95.0 percent of ss who use MJ almost daily. There is a similar, though not as striking, relationship between frequency of MJ use and "still using other drugs."

These results cannot be taken as evidence that MJ leads to use of other drugs; we have no information about which came first. It is evidence, in this sample, that ss who have never tried MJ (about half of the total) are unlikely to have tried anything else, and the likelihood of having tried other drugs is closely related to frequency of MJ use. Consequently in this report when we

speak of characteristics of frequent MJ users, we are clearly speaking of MJ-and-other-drug-users.

Demographic variables. Many of the descriptive variables included in the questionnaire have a significant relationship to frequency of MJ use. As would be expected, MJ use is related somewhat to age, the older subjects being more likely to have tried MJ but not necessarily to be using it more often. Males use MJ more often than females, but there is a great deal of overlap in the two distributions. Most of our ss are single and have not had military service, so that the relationship to MJ of these variables could not be studied. Daily MJ users were much more likely to live off-campus than on-campus (78.3 percent); the other user or non-user groups did not differ. MJ users are somewhat more likely to live in a group than alone. Among the undergraduates, frequency of use rises with class status; graduate and special students, however, are no more likely to use MJ than are freshmen.

Comment

These results confirm and extend our earlier findings that there are definite personality differences associated with frequency of use of marijuana. The differences are small but real. The study provides no way of knowing whether marijuana use preceded or was a consequence of the psychological differences. (In a separate study the long range effects of marijuana use are being investigated).

The marijuana users in this sample have not dropped out. They are goal-oriented, motivated, identified with parents, generally law-respecting, and reasonably well-adjusted. True, they are less so than their non-user fellow students; perhaps they have always been so, or perhaps the use of marijuana has made them so. They are more likely to question their emotional adjustment (even though they appear to be within the normal range) and also to question their parents' getting along. They are somewhat more depressed, despite the marijuana "high." If marijuana in this group represents an escape from personal problems, it is not an effective escape; if it creates problems instead, those that have been created are thus far not very visible. These students do not present the picture of a dropout who is unambivalently searching for pleasure, but of a somewhat troubled, questioning youth

who has basically the same values as his non-using peers.

Robbins et al³ found the typical MJ user to be a liberal arts major who reported somewhat looser religious ties than his non-drug-using classmates. He was more often anxious, bored, cynical, disgusted, impulsive, moody, rebellious and restless, dissatisfied with his school, less likely to be doing as well as others. The non-user, on the other hand, was more likely to describe himself as ambitious, contented, decisive and secure.

It may be, as Robbins and his coworkers were careful to point out, that non-users of MJ have a greater tendency to describe themselves along conventional socially acceptable lines and that users have a different set of norms—with their ideal image more that of a searching restless person. Perhaps in this respect they are, as Braiman⁹ suggested, like the alienated students Keniston¹⁰ described: "They are quick to admit their confusions, angers, anxieties and problems. Given a host of neurotic symptoms, they check them all, describing themselves as socially undesirable, confused, depressed, angry, neurotic, hostile and impulsive."

To them, their self descriptions do not necessarily imply maladjustment, but greater self awareness and honesty. Many of the virtues of the past are no longer regarded as virtues. There are altered attitudes toward work, sacrifice and success.

Liebert¹¹ suggests that, these days, if a young male goes through four years of college without having experienced marijuana, some might feel he had a rigidity of character structure and a fear of his impulses that was hardly desirable. Liebert refers, however, to the "heads" at the other end of the spectrum—the daily users who isolate themselves in the campus "head" subculture and who are obsessed with the mystique of "the experience" and who are alienated from any sense of mutuality with the vast majority of fellow students, faculty and administration. Liebert was more impressed with their boredom than their depression and, in contrast to others, found them with "a lack of awareness of internal states of feeling and an inability to describe them which is in sharp contrast to their articulateness in criticizing contemporary society."

For the most part, the personality differences we found are most noticeable in the group of students who use MJ weekly or daily, as one might expect. But the typical MJ user in this sample uses it only occasionally and is by no means representative of all MJ users. All of the ss in our sample were, after all, functioning well enough to be in college. The sample did not include those who had dropped out of high school or college or had gotten into trouble with the law. Any attempt to define or describe the personality of individuals who smoke marijuana will be as futile as attempting to describe the personality of people who drink. As with alcohol, the users of marijuana may be distributed on a continuum from the very occasional user to the chronic abuser whose life revolves about and is visibly affected by the use of MJ (along with other drugs) and the personalities would undoubtedly vary from one extreme to the other of the continuum. Of greater immediate importance is the need to determine the effect of marijuana use on the various personality types.

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Myocardial Infarction and Carbohydrate Metabolism Relating to Diabetes Mellitus

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■ *Fifteen non-obese males with acute myocardial infarction and no diabetic history were evaluated for diabetes. During infarction, results of oral glucose tolerance tests were "diabetic" or "probably diabetic" in 10 of the 15 patients (67 percent). The plasma immunoreactive insulin response in 12 patients (80 percent) was of a pattern observed in patients with maturity-onset diabetes. Six months after infarction, follow-up glucose tolerance tests in 12 surviving patients were diabetic or probably diabetic in three cases (25 percent). In seven of twelve patients (58 percent) had delay in the peaking of the plasma insulin response to an oral glucose tolerance test, a phenomenon that is observed in patients with maturity-onset diabetes.*

Glucose tolerance tests were abnormal in one of fourteen control subjects (7 percent). There was a delayed plasma insulin response to an oral glucose test in two of fourteen controls (14 percent).

Patients with myocardial infarction have an increased incidence of diabetes mellitus.

HYPERGLYCEMIA IS OFTEN associated with acute myocardial infarction.¹⁻³ Its significance and relationship to diabetes mellitus is controversial. The following study was undertaken to evaluate whether acute myocardial infarction unmasks latent diabetes mellitus.

Methods

Fifteen men, mean age 55.3 years (range 38 to 72), who had an acute transmural myocardial infarction uncomplicated by congestive heart failure or shock and 14 male control patients, mean

age 55.6 years (range 38 to 72), were the subjects in this study. None of the patients had liver, renal or thyroid disease nor were any taking drugs except for analgesics at the time of the study. All patients weighed less than 115 percent of their ideal body weight as indicated in the Metropolitan Life Insurance Company weight tables. Patients with a history of diabetes or a family history of diabetes mellitus were excluded from the study. All patients with myocardial infarction had an oral glucose tolerance test performed within 36 hours of their infarction, with plasma glucose, plasma insulin, and fasting plasma cortisol determinations made. The glucose load used was 100 grams. Ten of these patients also had fasting plasma growth hormone deter-

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TABLE 1.—*Plasma Glucose, Insulin, Cortisol and Growth Hormone Levels During Acute Myocardial Infarction and Follow-Up Studies*

Patient	Age	Glucose	Oral Glucose Tolerance Tests			Glucose	Six Months After Infarction	
			During Infarction				IRI	F
			IRI	F	GH			
1	38	PD	AB	H	N	N	AB	N
2	44	N	N	H	—	N	N	N
3	47	PD	AB	H	N	D	AB	N
4	49	D	AB	N	N	N	N	N
5	53	N	AB	H	N	N	N	N
6	53	PD	AB	H	N	N	AB	N
7	54	PD	AB	H	N	N	AB	N
8	55	N	N	H	—	N	N	N
9	57	N	AB	N	—	PD	AB	N
10	59	D	AB	N	N	PD	AB	N
11	64	N	N	H	N	N	N	N
12	45	D	AB	H	—	died		
13	67	D	AB	H	—	died		
14	72	D	AB	H	N	N	AB	N
15	72	PD	AB	H	N	died		

D = Diabetic
PD = Probably Diabetic
N = Normal
H = Abnormally High

IRI = Plasma Immunoreactive Insulin
AB = Abnormal
F = Fasting Cortisol Level
GH = Fasting Growth Hormone Level

minations performed at the time of their glucose tolerance test.

Three patients died of another myocardial infarction three to five months after the initial infarction. The 12 surviving patients had oral glucose tolerance tests with plasma glucose, plasma insulin, and fasting plasma cortisol levels performed six months after their acute infarction.

The 14 control patients had oral glucose tolerance tests with plasma glucose and plasma insulin determinations made.

Plasma was analyzed for glucose by the potassium ferricyanide oxidation-reduction method adapted for the autoanalyzer,⁴ insulin and growth hormone by the simultaneous double-antibody procedure of Morgan,⁵ and cortisol by the method of Mattingly.⁶ All determinations were made in duplicate.

Glucose tolerance tests were interpreted as normal, probably diabetic, or diabetic, according to the criteria of Fajans and Conn⁷ multiplied by a correction factor of 15 percent because plasma rather than whole blood was used.

The plasma insulin response to the oral glucose tolerance test was considered compatible with maturity-onset diabetes if either delayed peaking occurred with peak insulin response at two or three hours or if the serum insulin level exceeded the mean plus two standard deviations

of the control group's value for any given interval during the glucose tolerance test.⁸⁻¹¹

Results

Table 1 shows the results of the oral glucose tolerance tests with plasma glucose, plasma immunoreactive insulin, and fasting plasma cortisol determinations made during the acute infarction and six months afterwards and also fasting growth hormone determinations made during the acute infarction.

During the acute infarction, five of fifteen patients (33 percent) had a normal glucose tolerance curve, five had a probably diabetic curve, and five had a diabetic curve. Twelve out of fifteen patients (80 percent) had an abnormal plasma immunoreactive insulin response compatible with maturity-onset diabetes mellitus. Three out of fifteen patients (20 percent) had both a normal glucose tolerance curve and a normal plasma insulin response. Twelve (80 percent) had elevated fasting plasma cortisol levels. Ten out of ten patients had normal fasting growth hormone levels.

Six months after the acute infarction, one of the twelve surviving patients (8 percent) had a diabetic glucose tolerance curve, two (17 percent) had a probably diabetic glucose tolerance curve, seven (58 percent) had delayed peaking

of the plasma immunoreactive insulin response compatible with maturity-onset diabetes, five (42 percent) had both a normal glucose tolerance curve and a normal plasma insulin response, and all twelve had normal fasting plasma cortisol levels.

Table 2 shows the results of the oral glucose tolerance tests with plasma glucose and immunoreactive insulin levels determined in 14 control subjects. One out of 14 patients (7 percent) had a probably diabetic glucose tolerance curve, two (14 percent) had delayed peaking of the plasma insulin response compatible with maturity-onset diabetes, and 11 (79 percent) had both a normal

glucose tolerance test and a normal plasma insulin response.

Table 3 reveals the mean plasma glucose, insulin, cortisol, and growth hormone levels in the patients during and after myocardial infarction and in the control subjects.

T tests were computed between the mean plasma glucose and mean plasma insulin values of the oral glucose tolerance tests for the 15 patients during the acute myocardial infarction compared with the 14 control subjects, for the 12 surviving patients during and six months after the acute infarction, and for the 12 follow-up patients compared with the 14 control subjects. No significant differences were found except for the following:

1. The mean 60-minute plasma glucose value was higher during the acute myocardial infarction group than in the control group ($P < .02$).

2. The mean 120-minute plasma glucose value during the acute infarction group was higher than in the control group ($P < .01$).

3. The 120-minute plasma insulin value was higher during the acute infarction group than in the control group ($P < .01$).

The mean 120-minute plasma insulin value in the six-month follow-up group was or 166 percent that of the control group. However, this was not statistically significant because of the wide variation in plasma insulin values.

The mean fasting plasma cortisol value during the acute infarction was significantly higher than

TABLE 2.—Plasma Glucose and Insulin Levels in Control Subjects.

Patient	Age	Oral Glucose Tolerance Tests	
		Glucose	IRS
1	38	N	N
2	46	N	N
3	48	N	N
4	50	N	AB
5	59	PD	N
6	54	N	N
7	55	N	N
8	40	N	N
9	57	N	N
10	59	N	N
12	71	N	N
11	59	N	AB
13	72	N	N
14	71	N	N

D=Diabetic
PD=Probably Diabetic
AB=Abnormal

N=Normal
IRI=Plasma Immunoreactive Insulin

TABLE 3.—Mean Plasma Glucose, Insulin, Cortisol and Growth Hormone Levels During and After Myocardial Infarction and in Control Subjects

	Oral Glucose Tolerance Test										Fasting Plasma Cortisol in $\mu\text{g}/100\text{ ml}$ \pm one SD	Fasting Plasma Growth Hormone in nanogram/ml \pm one SD
	Plasma Glucose in $\text{mg}/100\text{ ml}$ \pm one SD					Plasma Immunoreactive Insulin $\mu\text{ units}/\text{ml}$ \pm one SD						
	Fasting	30 min	60 min	120 min	180 min	Fasting	30 min	60 min	120 min	180 min		
Within 36 Hours of Acute Myocardial Infarction	81 \pm 27	139 \pm 52	165 \pm 51	146 \pm 55	115 \pm 65	32 \pm 20	83 \pm 57	110 \pm 91	130 \pm 94	91 \pm 88	41 \pm 10	3.4 \pm 3.1
Six Months After Myocardial Infarction	72 \pm 13	118 \pm 30	132 \pm 38	103 \pm 39	71 \pm 31	25 \pm 13	64 \pm 44	74 \pm 35	78 \pm 62	43 \pm 20	22 \pm 6	
Control Subjects	79 \pm 13	131 \pm 21	126 \pm 24	93 \pm 17	82 \pm 20	32 \pm 12	69 \pm 26	84 \pm 39	47 \pm 19	50 \pm 29	19 \pm 9	3.9 \pm 3.5

in the controls ($P < .001$) and significantly higher than in the six-month follow-up group ($P < .001$). There was no significant difference between the mean plasma cortisol levels in the patients studied six months after infarction compared to the control subjects.

Discussion

In a previous report,¹² 12 out of 22 patients (55 percent) with coronary artery disease, including 21 patients with a previous myocardial infarction, who were evaluated for drug therapy in angina pectoris had an abnormal oral glucose tolerance test, and nine of these 22 patients (41 percent) had diabetes mellitus, according to the criteria of Fajans and Conn.⁷ In the present study, which excluded patients with known diabetes and with a family history of diabetes, 67 percent of the group had an abnormal oral glucose tolerance test during the acute infarction, and 25 percent of the survivors had an abnormal oral glucose tolerance test six months after the infarction.

Eighty percent of the patients during the acute infarction had an abnormal plasma insulin response to the oral glucose tolerance test, with a pattern that has been observed in patients with maturity-onset diabetes.⁸⁻¹⁰ None of these patients was obese, which could account for this type of plasma insulin response.¹³ In ten patients, there was delayed peaking with a maximum insulin response at 120 minutes. In two patients, there was a very high insulin response at 60 minutes. Both of these patients showed a delayed insulin peak at 120 minutes in the six-month follow-up oral glucose tolerance test.

Six months after the acute myocardial infarction, seven of twelve patients (58 percent) had delayed peaking of the plasma insulin response, a pattern observed in patients with maturity-onset diabetes. Tzagournis et al reported that 30 of 50 (60 percent) young patients with coronary heart disease had abnormally elevated or delayed insulin responses after an oral glucose tolerance test.¹¹

Although the mean plasma insulin response at 120 minutes in the survivors six months after their infarction was 166 percent that of the control group, this was not statistically significant because of the wide variation in plasma insulin levels. According to Berson and Yalow: "In non-obese, nondiabetic subjects the standard deviation of the plasma insulin concentrations are almost equal to the mean values . . . due to biologic variation and not to imprecision in the measurements of plasma insulin."¹⁴

One of the 14 (7 percent) control subjects had an abnormal glucose tolerance curve, and two (14 percent) had a delayed plasma insulin peak at two hours. This is compatible with Cerasi and Luft's findings that 15 of 85 (18 percent) unselected healthy adults with normal glucose tolerance had a plasma insulin response similar to that found in prediabetic and diabetic patients.¹⁵

Excessive secretion of growth hormone may induce impaired glucose tolerance and insulin resistance but is not a feature of maturity-onset diabetes.¹⁴ Fasting growth hormone was found to be normal in all ten patients in whom this determination was made during the acute infarction. Lebovitz et al also found, in patients with acute myocardial infarction, normal fasting plasma growth hormone levels.¹⁶ In addition, these investigators found an increase in growth hormone secretion after an intravenous glucose tolerance test in 12 of 18 patients (67 percent).¹⁶

Excessive catecholamine secretion due to stress was not responsible for the abnormal plasma insulin curves, since Porte et al have reported that epinephrine infusion causes an inhibitory effect upon pancreatic insulin release.¹⁷

Twelve of 15 (80 percent) patients had elevated fasting plasma cortisol levels due to the stress of the acute myocardial infarction. It is of interest that the three patients with normal plasma cortisol values during the acute infarction all had an abnormal plasma insulin response, and that the three patients with a normal plasma insulin response all had elevated plasma cortisol values.

One may conclude from our data that the very high incidence of plasma glucose and plasma insulin abnormalities during acute myocardial infarction was due to unmasking latent diabetes mellitus by the stress of the infarction. One may also conclude that the persistence of a high incidence of delayed plasma insulin peaking to an oral glucose tolerance test six months after infarction is compatible with a high incidence of latent diabetes mellitus in these patients. Before making these conclusions, however, we felt that the plasma insulin response to a glucose load needed to be investigated in other chronic illnesses.

We investigated the plasma immunoreactive insulin response to an oral glucose load in 14 patients with non-coronary heart disease and found that eight of them (57 percent) also had a plasma insulin response compatible with maturity-onset diabetes.¹⁸

We have concluded from our glucose tolerance data reported here and elsewhere¹² in agreement with other workers¹⁻³ that there is an increased incidence of diabetes mellitus in patients who have had myocardial infarction. We have interpreted the high incidence of an abnormal plasma immunoreactive insulin response in patients with myocardial infarction as representing a nonspecific metabolic abnormality compatible with, but not diagnostic of, maturity-onset diabetes.

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SETTING LIMITS ON "LINUSOSIS"

What do you do if a child won't be parted from a dirty old blanket?

"Certainly you can wash the blanket and keep it clean and then probably not do anything about it until the child is two or three years old. At that point you can begin to discipline the habit. If the child is going to use the blanket, give him permission to do it but in a limited area. You can do the same thing for thumbsucking.

"If you tell the child that either one of these activities is perfectly okay as long as it's confined to his room, then he can go there and suck his thumb and drag his blanket as much as he likes. But when he comes out into the rest of the house, he must leave it in his room. By limiting these activities to a specified area where the child is by himself, the parents are less upset and the youngster can go suck his thumb or drag his blanket to his heart's content and then come out and live with the rest of the family."

—J. WARD STACKPOLE, M.D., Burlington
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Evaluation of the Role of Nitrogen Dioxide in the Development of Respiratory Diseases in Man

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IN RECENT YEARS, considerable evidence has accumulated indicating that nitrogen dioxide is a deleterious component of air pollutants.¹⁻⁵ Most of the evidence is descriptive and relates either human or animal exposure to some measurement of pulmonary dysfunction. It is implicit in these experiments that the measured abnormality eventually results in chronic pulmonary disease—for example, emphysema and bronchitis. Since these diseases affect approximately 4 percent of the population and their incidence is increasing,⁶ this postulated sequence of events is of paramount practical importance. This report will review the available knowledge concerning the relationship of exposure to nitrogen dioxide and respiratory diseases.

Respiratory Effects of Nitrogen Dioxide In Man and Non-human Animals

The deleterious effects of air pollution are due to the interaction of many pollutants in addition to nitrogen dioxide, and hence a realistic evaluation of the significance of nitrogen dioxide requires data obtained within this context. Unfortunately, the complexities involved in investi-

gating total atmospheres, have, in previous times, been insurmountable. As a result, epidemiological studies have usually contained measurements of only a few of the potential pollutants and experimental models have utilized artificial atmospheres in which nitrogen dioxide was the sole pollutant. It is anticipated that the engineering difficulties which have prevented measuring and simulating ambient atmospheres are near solution and in the future nitrogen dioxide will be studied in a more relevant manner.

Sources of Nitrogen Dioxide Contamination

Nitrogen dioxide enters the atmosphere as a by-product of natural gas combustion, following explosions, in industrial processes requiring the handling of nitric acid, and most importantly from burning petroleum in internal combustion engines. Effluent from gasoline engines contains nitric oxide, a minimally toxic pollutant which at ordinary temperatures is oxidized to the more toxic nitrogen dioxide. Although the complex photochemical reactions governing pollutant interactions are not well understood, sequences describing pollutant interaction have been delineated. According to Haagen-Smit and Wayne,² early morning automobile usage produces large quantities of nitric oxide and hydrocarbons. In the presence of sunlight, these products react, converting nitric oxide to nitrogen dioxide so that by mid-morning the atmosphere contains peak

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nitrogen dioxide and low nitric oxide levels. Subsequent irradiation of the nitrogen dioxide produces increasing concentrations of ozone during the afternoon and reduces the nitrogen dioxide to low levels. Late afternoon automobile traffic again produces large amounts of nitric oxide which reacts with the ozone to remove most of this pollutant, and then the nitric oxide continues to reaccumulate at a decreasing rate for the remainder of the night.

As the descriptive sequence indicates, in California the major source of nitrogen dioxide is combustion of automobile fuel; atmospheric concentrations increase in parallel with automobile ownership and use.³ Thermal power plants are a second, major source of nitrogen dioxide. In heavily industrialized areas these utilities produce 25 to 50 percent of the total oxides of nitrogen.³

Although cigarette smoke does not contribute significantly to atmospheric pollution, the high concentrations of nitrogen dioxide which it contains may contribute to the enhanced incidence of respiratory disease of smokers.⁷ The pathophysiology of this self-pollution is beyond the scope of this review and will not be considered further.

Information Pertaining to Chronic Exposures in Man

The significance to human health of presently encountered atmospheric levels of nitrogen dioxide is not known.^{3,8} The older studies are difficult to evaluate because diagnostic criteria and data collection were inadequate.⁹⁻¹¹ Recent investigations involving healthy populations as well as patients with chronic respiratory diseases have yielded conflicting results. Shy et al compared neighboring communities in Chattanooga exposed to high and low concentrations of nitrogen dioxide.^{4,5} They reported a decrease in ventilatory performance and an excess of respiratory illness among families exposed to the increased levels of nitrogen dioxide. Since the source of nitrogen dioxide pollution was a factory producing trinitrotoluene (TNT), other automobile-associated pollutants such as carbon monoxide, hydrocarbons and lead were not considered factors in this study. Spicer and Kerr on the other hand measured pulmonary vital capacity, total lung capacity, functional residual capacity and airway resistance at weekly intervals in 100 seminary stu-

dents and did not find changes related to atmospheric concentrations of nitrogen dioxide.¹² The effect of exposure to ambient levels of oxidant including nitrogen dioxide on pulmonary function in patients with chronic obstructive respiratory disease has also been investigated.¹³⁻¹⁶ In two of these studies pulmonary function was evaluated during alternating periods in which patients breathed Los Angeles smog for a week and then decontaminated air for a week, and in both studies improvement in respiratory function was noted when the patients breathed decontaminated air.^{13,14} Objective measurements showing improved ventilatory function were the 3-second timed vital capacity, maximal breathing capacity, and a reduced residual lung volume.¹³ It is important to note that particulates and ozone as well as nitrogen dioxide were removed by the purification procedures, and hence these results may not pertain directly to nitrogen dioxide. Rokaw and Massey observed a group of 25 patients with chronic obstructive disease for 18 months and did not find a correlation between air pollution levels including nitrogen dioxide and subjective or objective measurements of pulmonary function.¹⁵ Burrows and coworkers in a larger but less precise investigation also failed to find significant relationships between air pollutant levels and pulmonary function in patients with chronic obstructive pulmonary disease.¹⁶

Acute Exposures in Man

Definitive evidence demonstrating that exposure to nitrogen dioxide can be deleterious to respiratory function comes from two sources. Acute exposure of humans to high levels of nitrogen dioxide invariably results in respiratory disease.¹⁷⁻²² In experimental animals exposed to elevated levels of atmospheric nitrogen dioxide pathologic changes resembling emphysema develop and susceptibility to bacterial infection is enhanced.²³⁻³⁴

The average level of nitrogen dioxide in atmosphere of smog-ridden areas of California is 0.25 ppm.² Air pollution surveys indicate a maximal concentration of 3.5 ppm of nitrogen dioxide.²³ Acute exposure to higher levels of nitrogen dioxide is an uncommon occupational hazard of workers manufacturing nitric acid,¹¹ of farmers (exposed to silage-silo-fillers' disease),^{17,18} and of electric arc workers.¹⁹ A range

of adverse effects correlating with the degree of exposure have been described. Eye and nasal irritation occurs after exposure to 15 ppm of nitrogen dioxide. Pulmonary discomfort is noted at levels of 25 ppm and bronchiolitis with focal pneumonitis occurs after exposures of 25 to 75 ppm of nitrogen dioxide. The duration of these exposures was put at less than one hour. Comparably short periods of exposure to 150-200 ppm causes fatal pulmonary fibrosis. Higher exposures are associated with acute pulmonary edema, sometimes death.^{1,17} These studies demonstrate conclusively that elevated concentrations of nitrogen dioxide are extremely toxic to human respiratory tissues.

Volunteer studies further support the hypothesis that acute exposure to concentrations of nitrogen dioxide above ambient, will impair pulmonary function. Abe²⁰ observed an increased expiratory and inspiratory flow resistance in healthy adults exposed for 10 minutes to 4 to 5 ppm of nitrogen dioxide. Higher levels of exposure (50 ppm) for 1 minute have been shown to cause significant nasal irritation and pulmonary discomfort.²¹

Animal Experiments

The heightened contemporary interest in the potential toxicity of nitrogen dioxide has led to many investigations with experimental animals. These experiments have certain inherent deficiencies. In most cases, the animal model is similar but not completely analogous to the human. As an example, the respiratory anatomy of rats (the animal most frequently used in studies of nitrogen dioxide induced emphysema) differs from that of humans in: not having interlobular septae; having fewer generations of airways; utilizing distal bronchioles for respiration rather than alveoli; pulmonary vasculature.³⁵ The epithelium of the tracheobronchial tree of rats also differs from man in that it has more large, mucus-secreting glands lining the trachea and fewer along the bronchi.³⁶ There are also important anatomic differences between humans and rabbits, mice, guinea pigs, monkeys, and dogs.³⁵ These distinctions in anatomy may explain why identical concentrations of nitrogen dioxide cause diverse pathologic disturbances and make interpretation that is relevant to disease in man exceedingly difficult.

Pathologic Abnormalities Following Exposure to Nitrogen Dioxide

Most studies concerned with the pathology of prolonged exposure to nitrogen dioxide have utilized rodents.^{28-30,32,37,38} In rats exposed to 10, 12.5, or 25 ppm of nitrogen dioxide for three or more months the thoracic cavities become larger, dorsal kyphosis develops and the animals have an inflated appearance. Microscopically there is distension of alveolar ducts, dilation of alveoli and hyperplasia of bronchiolar epithelium. Alveolar septa are occasionally missing, but destruction of parenchyma is unusual.^{30,37} These pathologic features are similar but not identical with those of human emphysema. A critical difference is the absence of alveolar necrosis. Destructive bullous lesions are the *sine qua non* of emphysema;³⁹ bullae are absent in rodent models. Also, it should be noted that the lesions mentioned above do not develop in rats exposed to lower concentrations of nitrogen dioxide (0.8 to 2.0 ppm) for their entire lifetime. The lungs from these animals are grossly normal; microscopic examination shows only minor degrees of ciliary loss, epithelial hypertrophy and "cytoplasmic blebbing."^{32,38} These animals live out a normal life span and die of diseases unrelated to nitrogen dioxide.³⁷

Mice are more susceptible to the toxic effects of nitrogen dioxide than rats. Continuous exposure to 0.5 ppm of nitrogen dioxide for three months causes loss of cilia, alveolar cell disruption and obstruction to respiratory bronchioles.³¹ Exposures of longer duration cause more severe changes and pneumonitis.³¹ These pathologic abnormalities are, however, unlike the changes of emphysema in man.

Haydon et al exposed rabbits continuously to atmospheres containing 8 to 12 ppm of nitrogen dioxide for 3 to 4 months and reported destructive changes in alveolar walls and abnormal enlargement of the distal air spaces.²⁷ These findings closely approximate the emphysematous lesions observed in humans. Unfortunately, there are no reports of data obtained from rabbits exposed to lower concentrations of nitrogen dioxide. It should also be noted that other investigators have failed to find emphysematous changes in rabbits exposed for two hours per day to 15 to 25 ppm of nitrogen dioxide for periods up to two years.⁴⁰ A multifocal type of emphysema

has been induced in guinea pigs following three weeks of exposure for two hours daily to 22 ppm of nitrogen dioxide.⁴¹ Since these levels are considerably above ambient, the relevance of this model to human disease states is doubtful. The hamster appears to be particularly resistant to the toxic effects of nitrogen dioxide. Kleinerman and Cowdry exposed hamsters to 45 to 55 ppm of nitrogen dioxide for 21 to 23 hours daily for ten weeks and did not find emphysematous changes.⁴⁰ The dog is also resistant to the toxic effects of nitrogen dioxide. Wagner et al exposed dogs to 5.0 ppm of nitrogen dioxide for 15 to 18 months and did not find differences between the lungs of treated and control animals.³⁴ These distinctive results have been confirmed by other investigators.^{28,33} Investigations with monkeys are currently in progress but have not yet been reported.⁴² Horses, the laboratory animals whose pulmonary anatomy most closely approximates that of man, have, apparently, not been studied.

Effect of Nitrogen Dioxide on Pulmonary Resistance to Infection

Ehrlich and coworkers in a series of experiments have shown that acute and chronic exposure to relatively low levels of nitrogen dioxide depresses pulmonary resistance to infection in mice.^{23,24,31} The experimental method consisted of exposing animals to atmospheres of fixed nitrogen dioxide concentration before infection with aerosols of virulent *Klebsiella* sp. The technique has been sufficiently standardized to predict that 25 to 50 percent of infected controls will die of pneumonia caused by the *Klebsiella* sp. within 14 days. In a few experiments, bacterial clearance rates were obtained by removing lungs at various time intervals after infection and determining the concentrations of bacteria.

In the acute experiments, mice were exposed for two hours to concentrations of nitrogen dioxide (1.5 to 25 ppm) before infection. Significant increases in mortality occurred in the animals exposed to levels above 3.5 ppm. Deaths did not occur in uninfected mice exposed to identical concentrations of nitrogen dioxide.²³ Further studies with this murine model showed that the adverse effect of nitrogen dioxide is transient. Animals infected with virulent *Klebsiella* microorganisms 27 hours after exposure to 5, 15 or 25 ppm of nitrogen dioxide did not have an increased mortality when compared with controls.

These investigators also showed that continuous exposures to levels of nitrogen dioxide only slightly above ambient (0.5 ppm or more for three months) depressed murine resistance to pulmonary infection.²⁴

Studies of pulmonary bacterial clearance mechanisms using the previously mentioned bacterial clearance technique have demonstrated that the enhancement of murine susceptibility to infection by *K. pneumoniae* was caused by diminished pulmonary antibacterial activity. Mice which are exposed to nitrogen dioxide and then challenged with aerosols of *K. pneumoniae* are unable to kill the inhaled bacteria as well as untreated controls. This decrease in bacterial clearance rate is directly proportional to the intensity of exposure to nitrogen dioxide.

Experiments in which hamsters were exposed to nitrogen dioxide and then infected with aerosols of *Klebsiella pneumoniae* also demonstrated impairment in pulmonary clearance mechanisms, but only at very high concentrations of nitrogen dioxide.²³ This relative increase in resistance to the effect of nitrogen dioxide exposure was attributed to both a diminished virulence of *Klebsiella pneumoniae* for hamsters and an increased resistance to the adverse effects of nitrogen dioxide.

A few experiments with monkeys have been performed.^{25,43} A two hour exposure to 10 to 50 ppm of nitrogen dioxide depressed resistance to aerosol challenge with *Klebsiella pneumoniae*.⁴³ Exposure to 10 ppm of nitrogen dioxide for one month or 5.0 ppm for two months also resulted in an enhanced susceptibility to infection. The latter data are preliminary since only a few monkeys were studied; thus, one of four monkeys died following exposure to 10 ppm of nitrogen dioxide and two of seven died at the 5.0 ppm level.²⁵

The effect of nitrogen dioxide in combination with other pollutants has been studied by Coffin and coworkers.⁴⁴ In these studies, exhaust from an automobile was photochemically treated and conveyed into exposure chambers. Mice within the chambers were exposed to the auto exhaust for four hours and then infected with aerosols of *Streptococcus*. An enhanced mortality was noted in animals exposed to 25 ppm of carbon monoxide and 0.15 ppm of oxidant. Since nitrogen dioxide forms a significant percentage of exhaust oxidant, it is likely that in this situation it contributed to the adverse effect.

In one report, exposure to nitrogen dioxide did not cause a decrease in pulmonary anti-bacterial activity.⁴⁵ Buckley and Loosli exposed germfree and conventional mice to 38 ppm of nitrogen dioxide for six weeks. At the end of this period the animals were infected with aerosols of *S. aureus*, and bacterial clearance rates were determined during the next five days. Although the rates of bacterial clearance for the germfree and conventional mice differed, neither group was affected by exposure to nitrogen dioxide. The investigators interpreted their data as showing that nitrogen dioxide did not effect bacterial clearance rates. These studies may be criticized on two counts. First, only three animals were studied at each time period—too few for statistical analysis. Second, *S. aureus* is not pathogenic for mice. Within 24 hours, 99 percent are removed and hence significant differences in clearance that might have occurred within the initial 24-hour period would have been overlooked.

It should be noted that it is very unlikely that the differences in the data of these studies were due to the kinds of microorganisms that were studied (that is, the pathogen *K. pneumoniae* and the non-pathogen *S. aureus*). Previous investigations with similar murine models have clearly shown that differences in bacterial virulence cause quantitative but not qualitative changes in clearance rates.^{46,47}

Effect of Nitrogen Dioxide on Alveolar Macrophage Function

From the previously cited *in vivo* studies, exposure to nitrogen dioxide appears to inhibit alveolar macrophage function.^{23,25,31,43} A few studies have been reported in which macrophages were exposed to nitrogen dioxide *in vitro*.^{48,49} According to the data from one investigation, macrophages are killed by exposure to extremely high levels of nitrogen dioxide, 176 ppm.⁴⁸ Myrvik and Evans, in a more elegant study, exposed alveolar macrophages from rabbits to 50 ppm of nitrogen dioxide and demonstrated a significant reduction in phagocytic function with a concomitant suppression of cellular energy pathways.⁴⁹ Before evaluating data obtained from *in vitro* exposures to nitrogen dioxide, it should be recognized that the effective concentration of nitrogen dioxide in the fluid phase is undoubtedly much lower than in the air

phase due to the instability of nitrogen dioxide in water. Hence the atmospheric concentrations used cannot be equated with the levels reported in *in vivo* experiments.⁴⁹

Effect of Nitrogen Dioxide On Mucociliary Function

Few studies relating exposure to nitrogen dioxide to mucociliary function have been performed.⁵⁰⁻⁵² According to the data obtained, ciliary activity is inhibited by exposure to nitrogen dioxide and this defect results in a decreased rate of particle removal. Certain deficiencies in the laboratory model deserve emphasis. Clearance rates were measured in isolated tracheal segments from either rabbits or rats. An isolated segment is divorced from neuromuscular control, blood supply and the effects of deglutition. Moreover, the rate that particles move along the trachea may not be representative of the rate of function of the entire tracheobronchial tree. Finally, the nitrogen dioxide exposures were short-term and at levels considerably above ambient.

Recently, an improved method of studying mucociliary function has been reported by Spritzer and coworkers.⁵³ A tight-fitting tube is inserted surgically into the esophagus of the rat and then attached, via the stomach, to an external collecting bottle. Radiolabeled particles are either aerosolized or injected intratracheally and the rate of entrance into the collection bottle is measured. Curves of particle removal for "normal" rats have been reported. Further experiments with this model should allow a more accurate determination of the effect of nitrogen dioxide on mucociliary function.

Effect of Nitrogen Dioxide On Immune Mechanisms

In preliminary studies nitrogen dioxide appears to have an effect upon immune reactions. Matsuura recently demonstrated that exposure of guinea pigs sensitized to egg albumin to 70 ppm of nitrogen dioxide for 30 minutes enhances their susceptibility to systemic anaphylaxis when challenged with aerosols of egg albumin.⁵⁴ Exposure to lower concentrations of nitrogen dioxide (40 ppm) causes an increase in the severity of the dyspneic symptoms.⁵⁵ Circulating antibody reactive with pulmonary tissue has also been found in guinea pigs that were exposed for as long as

one year to 5.0 to 15.0 ppm of nitrogen dioxide.⁵⁶ Since these experiments were conducted at pollutant exposure levels much above ambient, further investigations will be necessary before these data can be related to human instances of pulmonary disease.

Nitrogen Dioxide as a Biological Oxidant

The biochemical mechanisms by which nitrogen dioxide causes cellular dysfunction are in the initial stages of investigation. Since nitrogen dioxide and ozone are similar, it may be that some of the toxic effects of nitrogen dioxide result from biological oxidation to form free radicals.¹ Thomas and associates have presented evidence to support this important hypothesis.⁵⁷ These investigators showed an increase in lipoperoxidation of lung lipids in rats exposed to 1.0 ppm of nitrogen dioxide four hours daily for six days. Of practical significance is the additional finding that pre-treatment with high levels of anti-oxidant (10 mg of vitamin E per day) was partially effective in preventing the lipid peroxidative changes induced by nitrogen dioxide. Although it is hazardous to extrapolate from data obtained in laboratory models of infection to instances of human disease, nevertheless these experimental results raise the intriguing possibility that the ingestion of anti-oxidants might prevent some of the deleterious consequences accruing from exposure to nitrogen dioxide.

Conclusion

The studies that have been cited document severe pulmonary disease in individuals exposed acutely to very high concentrations of nitrogen dioxide. However, these concentrations are much above ambient and their relevance to daily environmental exposures is minimal. Since concern about the potential danger of nitrogen dioxide is quite recent, and the postulated disease processes are chronic, definitive information relating pulmonary disease to exposure to nitrogen dioxide under actual, ambient conditions is not available.

There are epidemiological data, however, that support the idea that respiratory impairment may occur in healthy populations and in patients with chronic obstructive respiratory disease following exposure to atmospheric levels of nitrogen dioxide. Although not conclusive, this evidence is suf-

ficient to justify extensive epidemiological investigations designed to determine the significance to human health of exposure to ambient concentrations of nitrogen dioxide. Animal models have served as a valuable means for determining the pathophysiological effects of exposure to pollutants. These studies have shown that exposure to nitrogen dioxide in concentrations that exceed those ordinarily encountered results in pathologic abnormality of the bronchi and alveoli and an enhanced pulmonary susceptibility to bacterial infection.

At present, extrapolation from these data to man is hazardous since animal models do not truly reflect the environmental-host relationships of human exposure. However, as newer techniques are developed, quantitative data delineating the pathophysiological effects, if any, of ambient exposures to nitrogen dioxide should become available and allow insight into the biological consequences of chronic exposure of man to nitrogen dioxide.

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THYROID SUPPRESSION AFTER OPERATION FOR PAPILLARY CANCER OF THE GLAND

Do you use thyroid suppression therapy following operation for papillary cancer of the thyroid gland?

"Yes, I use it for two reasons. The primary reason is the fact that we've done total lobectomy on one side and a subtotal or partial on the other side, leaving 1 to 2 grams of thyroid tissue. This is usually insufficient in amount to prevent myxedema. For this reason, in order to keep the patient euthyroid, I use thyroid replacement therapy.

"Secondly, if by chance there is some truth to the fact that lesions are hormone-dependent, the patient is going to benefit in this respect also."

—OLIVER H. BEAHR, M.D., Rochester

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MEDICAL STAFF CONFERENCE

Acute Renal Failure — Diagnosis, Management and Pathogenesis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. HAVEL*: The first case for presentation at Grand Rounds today is that of a patient with acute renal failure who will be presented by Dr. Cuddihee from the Public Health Service Hospital.

DR. CUDDIHEE†: The patient is a 28-year-old white man who was in good health until, three days before admission, his right thigh was severely crushed. On admission to another hospital he had no detectable blood pressure. After 6 hours of resuscitative measures, including 19 units of whole blood and 2 units of dextran, his blood pressure was 120/80 mm of mercury. After blood pressure stabilized at that level, venograft on a completely severed right femoral artery was carried out.

The patient was anuric following the operation, and after three days he was transferred to Moffitt Hospital for treatment of acute renal failure. On admission, blood pressure was 160/100 mm of mercury, pulse 68 beats per minute, temperature 37.0° C (98.6° F) and respiration 20 per minute. The patient was not in acute distress but was somnolent and pale. Funduscopic examination was normal and neck veins were

not distended. The lungs were clear to auscultation and percussion; the heart rate was regular and no rubs or murmurs were heard. Diffuse tenderness throughout the abdomen was noted, but no rebound tenderness. The bowel sounds were normal and no organomegaly was present. There was a 13-inch laceration of the right thigh with avulsion and necrosis of muscles. The right foot was cool, mottled and pulseless.

The x-ray films on admission showed a long linear fracture of the right ilium and a long fracture with some displacement through the innominate portion of the pelvis. There was also a subtrochanteric fracture of the femur. A cystogram showed the bladder normal except for some diverticula. A retrograde urogram did not demonstrate extravasation of contrast material from the collecting system of the kidney.

The white blood cell count was normal but there was a greater than normal proportion of polymorphonuclear cells. The hematocrit was 24 volumes percent. Serum sodium was 132.0 mEq, chloride 92.0 mEq, HCO₃ 18 mEq and potassium 5.9 mEq per liter. Serum creatinine was 6 mg and the blood urea nitrogen (BUN) 96 mg per 100 ml. Specific gravity of the urine was 1.010. An intravenous injection of 12.5 grams of mannitol did not increase urine flow.

*Richard J. Havel, M.D., Professor of Medicine.

†Robert Cuddihee, M.D., Renal Fellow.

On the day of admission a Scribner arteriovenous shunt was inserted into the arm, and the following day hemodialysis was begun. On the fourth day after admission pseudomonas aeruginosa was cultured from the wound in the thigh, and gentamicin sulfate was given. Because of continued infection and gangrene the right leg was amputated above the knee on the ninth day in hospital. Later baeteroides was cultured from the amputation wound and chloramphenicol was administered. Another complication during the course of the acute renal failure was the development of hypertension, which was treated with methyldopa and removal of fluid by hemodialysis. On the 40th day in hospital, urine volume increased and the diuretic phase ensued with complete return of normal renal function.

DR. HAVEL: Today Dr. Schrier will discuss the various aspects of the management, treatment and pathogenesis of acute renal failure.

DR. SCHRIER:* Much of the interest and knowledge about acute renal failure has resulted from experience during the various wars. During the London blitz acute renal failure was associated with many crush injuries, and surveys after World War II indicated that the mortality from acute renal failure secondary to such trauma was as high as 90 percent.¹ These surveys also indicated that acute renal failure developed in about 10 to 20 percent of all casualties during the war. During the Korean War the mortality statistics were similar until specialized teams were sent to Korea and patients with acute renal failure were treated with hemodialysis. With the institution of hemodialysis by these specialized teams, the mortality of acute renal failure decreased from 90 percent to approximately 60 percent.²

During the two decades since the Korean War, this mortality rate for acute renal failure associated with trauma has remained relatively constant both in military and civilian population. However, these mortality statistics do not tell the entire story. Although the mortality rate in Viet Nam for traumatic acute renal failure still remains between 50 and 60 percent the incidence of acute renal failure has been greatly diminished. It develops in only 1 in every 1,867 patients with wounds inflicted in Viet Nam.³ This is in contrast to an incidence of 1 in 200 during the Korean

War,² and 1 in 10 during World War II.¹ This diminished incidence of acute renal failure in military casualties in Viet Nam doubtlessly results from rapid evacuation by helicopter and prompt resuscitative measures.

This sequence of historical events emphasizes the potential importance of prophylactic measures in preventing acute renal failure and moreover the necessity of understanding the pathogenesis of the disease.

Before turning to the pathogenesis, however, I would like to discuss several aspects of the diagnosis and management of acute renal failure of all varieties. First a definition: Acute renal failure is an acute impairment of renal function leading to accumulation of nitrogenous wastes in the body which is not reversible by manipulation of extrarenal factors. It has become increasingly apparent that, in contrast to earlier teachings, a daily urine volume of less than 400 ml is a poor definition of acute renal failure, since patients may become progressively azotemic while excreting 1500 ml of urine in 24 hours. The reason for this set of circumstances is illustrated by the following example. A patient with acute renal impairment may have to excrete an endogenous solute load of 600 milliosmoles per 24 hours, although the maximal urinary osmolality obtainable may only be 300 milliosmoles per kg of water. In this circumstance at least 2 liters of such isotonic urine must be excreted per day to eliminate the 600 milliosmoles of solute. Thus even with 1500 ml of isotonic urine per day progressive solute accumulation and azotemia will develop. This form of acute renal failure has become known as "acute non-oliguric renal failure" to differentiate it from acute oliguric renal failure in which the 24-hour urine volume is actually less than 400 ml per day.

I would also like to comment on the use of terms *acute renal failure* and *acute tubular necrosis*. Although most clinicians use them interchangeably, acute renal failure is a clinical diagnosis and acute tubular necrosis is a histological diagnosis. Recent studies by Finckh et al⁵ and also by Olsen and Skjoldborg⁶ have shown that there may be very little correlation between the histological presence of acute tubular necrosis and the clinical diagnosis of acute renal failure. In most cases of acute renal failure the kidneys are enlarged and edematous and on histological examination the tubules are found to be dilated

*Robert W. Schrier, M.D., Assistant Professor of Medicine.

and to contain pigment casts in the tubule lumens. The tubular epithelium on occasion has minimal changes of degeneration, but frank necrosis is extremely rare. In kidneys from patients with acute renal failure the ultrastructure of the tubules is also quite normal in appearance, with a normal brush border, normal basement membrane, and very well organized mitochondria and organelles throughout the cell. There is, in fact, very little disarray of the structure. Physicians who continue to use the terms interchangeably should do so with the understanding that *acute tubular necrosis* is a misnomer in most cases of *acute renal failure*.

Diagnosis of Acute Renal Failure

Before a diagnosis of acute renal failure is made, the possibility should be excluded that the azotemia is the result of extrarenal causes. Many of the causes of such "prerenal" failure are shown in Table 1. While diminished blood pressure due to hemorrhage and other causes of volume depletion are well recognized as factors in renal ischemia, it must be remembered that significant renal ischemia may occur with blood pressure normal but renal vascular resistance increased in association with anesthesia, surgical or other trauma or hepatorenal syndrome. The clinician should therefore not be surprised by the occurrence of oliguria in the absence of a history of a hypotensive episode, for renal blood flow can be impaired by a decrease in renal perfusion pressure or by an increase in renal vascular resistance.

In addition to an awareness of the clinical circumstances in which prerenal failure may occur, examination of the urine may be very helpful in distinguishing between prerenal failure and acute renal failure.⁷ If the azotemia is due to an extrarenal or prerenal stimulus, the renal tubules will be avidly reabsorbing sodium and the urinary sodium concentration will be less than 10 mEq per liter. For example, with hemorrhage renal ischemia occurs and is associated with an increase in renin, aldosterone and antidiuretic hormone. The presence of increased aldosterone activity accounts in large part for the low urinary sodium concentration and will also be associated with an increase in urinary potassium concentration. The release of antidiuretic hormone (ADH) also allows for the use of urinary osmolality as an index of tubular function. Since the ability to

TABLE 1.—"Prerenal" Causes of Renal Failure

Hypovolemia
Hemorrhage
Gastrointestinal losses
Burns
Trauma
Impaired Cardiac Function
Myocardial infarction
Pericardial tamponade
Acute Pulmonary embolism
Peripheral Vasodilatation
Bacteremia
Antihypertensive medications
Increased Renal Vascular Resistance
Anesthesia
Surgical operation
Hepatorenal syndrome
Renal Vascular Obstruction—Bilateral
Embolism
Thrombosis

TABLE 2.—"Postrenal" Causes of Renal Failure

Urethral Obstruction
Bladder Neck Obstruction
Prostatic hypertrophy
Bladder carcinoma
Bladder infection
Functional: Neuropathy or ganglionic blocking agents
Obstruction of ureters—bilateral
Intraureteral
Sulfonamide and uric acid crystals
Blood clots
Pyogenic debris
Stones
Edema
Necrotizing papillitis
Extraureteral
Tumor: Cervix, prostate, endometriosis
Periureteral fibrosis
Accidental ureteral ligation during pelvic operation

concentrate the urine is lost in acute renal failure, a urine osmolality which is greater than plasma osmolality supports a prerenal cause of the azotemia. The concentration of urea and creatinine in the urine and plasma may also be helpful in distinguishing prerenal failure from acute renal failure. In prerenal, or so-called functional renal failure, the ratio of urine to plasma creatinine and urea should be in excess of 14 to 1, thereby demonstrating the persistent ability of the kidney to concentrate and excrete these nitrogenous waste products.

In addition to differentiating prerenal causes of oliguria from acute renal failure, postrenal

TABLE 3.—Clinical Circumstances Associated with Acute Renal Failure

Sequelae of Prolonged "Prerenal" Failure
Nephrotoxins
Intravascular hemolysis
Obstetrical
Heat-stress and exercise
Idiopathic—25 to 30 percent
Miscellaneous

causes, such as obstruction, must always be considered (Table 2). Since patients with postrenal causes of oliguria may give very little clinical history suggestive of obstruction, this remediable cause of oliguria must be considered in every case of acute renal failure. However, a good clinical history may on occasion be helpful in suggesting the presence of urinary tract obstruction. For example retroperitoneal fibrosis may develop in a patient taking methysergide maleate for severe migraine headaches,⁸ or a patient with a long history of phenacetin ingestion may have acute papillary necrosis with obstruction.⁹ Obviously, urinary retention due to bladder neck obstruction is the most common cause of obstruction. Only after exclusion of both prerenal and postrenal causes of renal failure can the diagnosis of acute renal failure be considered. The most common circumstances in which acute renal failure is known to occur are shown in Table 3.

Management of Acute Renal Failure

In the management of acute renal failure, the physician has the choice between peritoneal dialysis and hemodialysis, either of which may be effectively used in treating a patient with acute renal failure. In circumstances of increased catabolism, almost continuous peritoneal dialysis may be necessary to decrease the azotemia. The persistently elevated diaphragms associated with the placement of the dialysis fluid in the abdomen, however, may lead to atelectasis and pulmonary infections.¹⁰ The incidence of peritonitis, the most frequent complication of peritoneal dialysis, also increases with the length of the dialysis.¹¹ Hence hemodialysis, rather than continuous peritoneal dialysis, should be used to control the azotemia in very catabolic patients. An example of a patient in whom continuous peritoneal dialysis was not sufficient to control azotemia is shown in Chart 1. The case was that of a military recruit with acute renal failure induced by heat

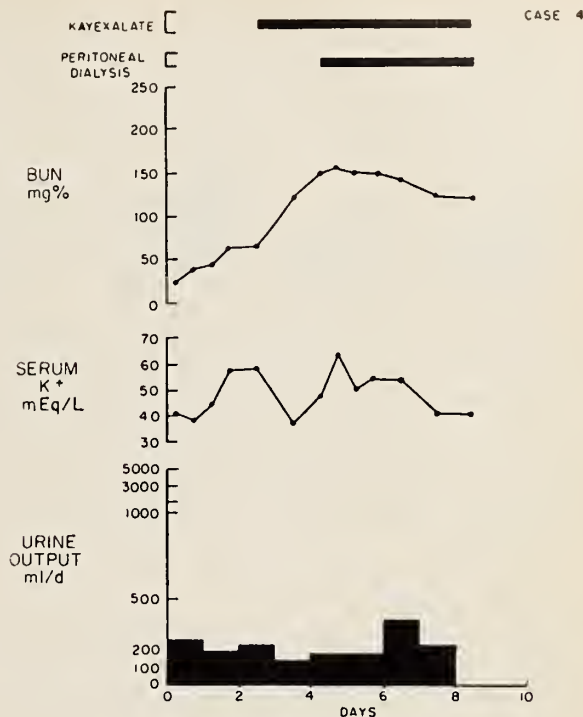


Chart 1.—Ineffective treatment of heat and exercise-induced acute renal failure with continuous peritoneal dialysis. The very catabolic patient was treated with peritoneal dialysis for 5 consecutive days without a substantial decrease in BUN and symptoms of uremia progressed during this period. (Reproduced by permission of the publisher.¹²)

and exercise.¹² Acute renal failure in this patient was associated with diffuse rhabdomyolysis and thus was very similar to acute renal failure associated with trauma. After five days of continuous peritoneal dialysis failed to decrease the azotemia, acute septicemia and hypotension developed and the patient died.

There are at least two potential causes for such inefficient peritoneal dialysis. As in the catabolic patient just mentioned, there can be an increased rate of production of urea and other nitrogenous waste products which may equal the rate of urea removal by peritoneal dialysis. The other cause of inefficient peritoneal dialysis is a decrease in urica clearance by the peritoneum due to splanchnic vasoconstriction or abnormalities in the peritoneal vasculature, such as may occur with intravascular coagulation, malignant hypertension and connective tissue diseases.¹³ It should also be appreciated, however, that independent of the rate of production or removal of urea, large persons have a larger urea space. Hence for the same peritoneal urea clearance a smaller fall in

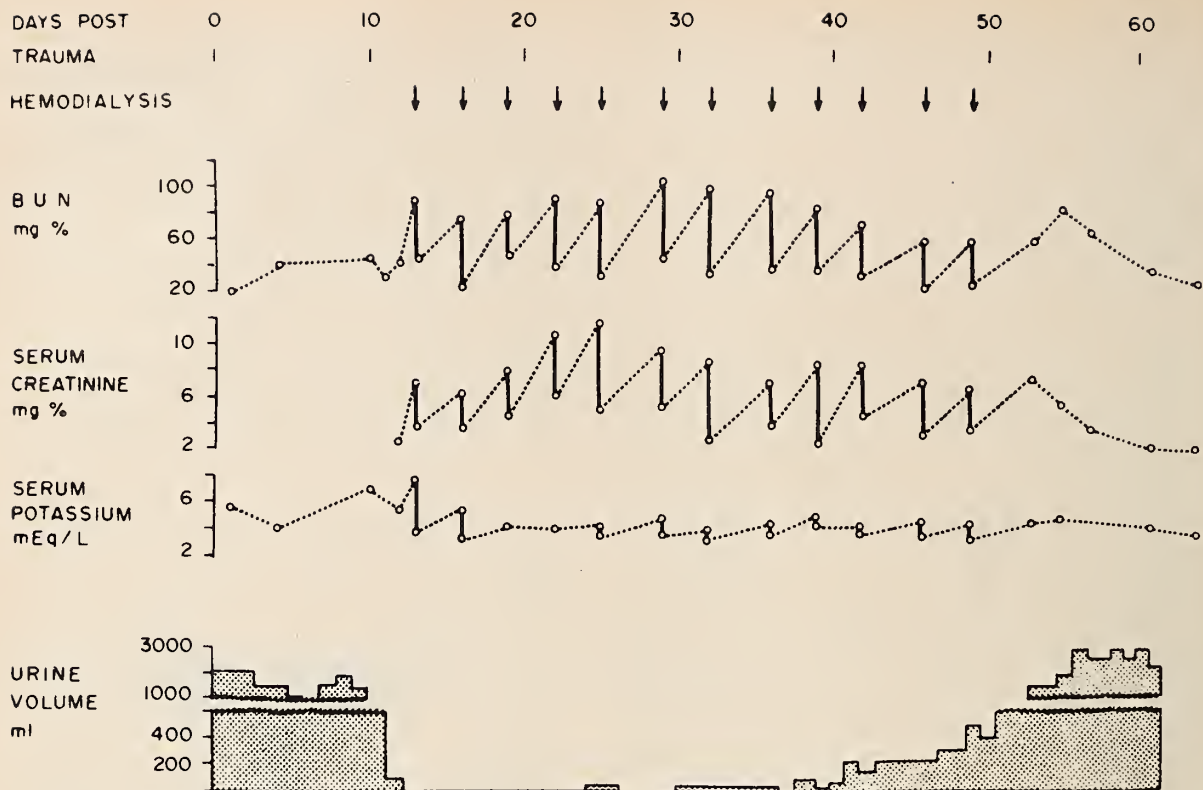


Chart 2.—Effective treatment of acute renal failure secondary to traumatic wounds. The patient, very catabolic, was treated with hemodialysis every other day so that the BUN and creatinine were never allowed to exceed 100 mg and 10 mg per 100 ml respectively, and uremic symptoms did not occur. (Reproduced by permission of the publisher.³)

BUN will occur in larger patients. Another consideration in estimating the expected decrement in BUN is the level of BUN before dialysis. Since the instillation, equilibration and removal rate of the dialysis fluid is generally the same during most peritoneal dialyses, the removal rate of urea is primarily determined by the urea concentration in the dialysis fluid after equilibration. Since this concentration is largely determined by the plasma-to-dialysis fluid gradient for urea, those patients with the highest initial BUN, and thus the largest plasma-to-dialysis fluid gradients, will have the highest urea concentrations in the dialysis fluid after equilibration and thus the greatest removal rate of urea. Therefore, patients who have the highest BUN levels before dialysis should be expected to have the largest decrements in BUN following dialysis.

On this background of factors that might contribute to inadequate or inefficient peritoneal dialysis, the criteria for adequate dialysis should be stressed. Dialysis should be used not only to treat the symptoms of uremia but also to prevent

the occurrence of these symptoms whenever possible. The term *prophylactic dialysis* has been used to describe this form of preventive treatment. Results of the effective use of prophylactic hemodialysis in a patient from Viet Nam who had acute renal failure secondary to trauma are shown in Chart 2. Hemodialysis was necessary every other day to maintain the BUN under 100 and creatinine between 6 and 10 mg per 100 ml. On this regimen, however, the patient did not manifest symptoms of uremia and after 34 days of dialysis he entered the diuretic phase of acute renal failure and ultimately recovered completely. There now seems to be considerable evidence that such use of prophylactic dialysis is associated with a decrease in both the morbidity and mortality of acute renal failure.^{14,15}

Pathogenesis of Acute Renal Failure

I would like to spend the remainder of the time discussing the potential pathogenetic factors which may be involved in acute renal failure. At one time the decrease in renal blood flow in

acute renal failure was considered of paramount importance.¹⁶ This tentative conclusion was due to the fact that para-aminohippuric acid (PAH) was used to estimate renal blood flow. Normally 90 percent of PAH is excreted in the urine and only 10 percent remains in the renal venous blood. In this circumstance the renal venous concentration can be considered to be zero and no large error is introduced by not collecting renal venous blood. In chronic renal disease and acute renal failure, however, the renal extraction of PAH may be as low as 25 percent, so that 75 percent of the PAH in the renal artery leaves the kidney by way of the renal vein rather than the urine. In these circumstances both the renal venous extraction and clearance of PAH must be measured for accurate assessment of renal plasma flow. When renal plasma flow was assessed only by the clearance but not extraction of PAH, acute renal failure seemed to be associated with near absence of renal plasma flow. When other methods, such as dye dilution technique and xenon washout curves, were used to measure renal blood flow in cases of acute renal failure and chronic renal failure, it was found that most patients with acute renal failure had a rate of renal blood flow which was about one-third of normal.¹⁷ Although this was a significant diminution, this renal blood flow was about the same as found during chronic renal failure (Chart 3). The fact that oliguria was present in acute renal failure but not in chronic renal failure therefore did not seem to be due to differences in total renal blood flow. Furthermore, total renal blood flow was found not to be significantly different during the oliguric and diuretic phase of acute renal failure, a finding which further suggested that factors other than total renal blood flow were involved in the pathogenesis of acute renal failure.

A redistribution of renal blood flow from the cortex to the medulla has, however, been suggested as an important factor in the pathogenesis of acute renal failure. Hollenberg and his colleague¹⁸ did renal arteriogram studies and xenon washout curves in a series of 20 patients with acute renal failure. In the renal arteriograms these investigators found that the terminal vasculature in the cortex does not fill during the oliguric phase and improved filling of this terminal vasculature occurs during the diuretic phase. The xenon washout curves also supported this

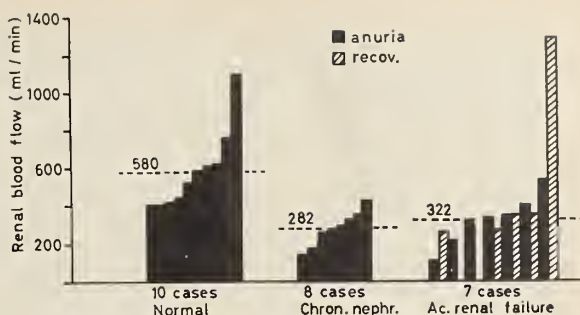


Chart 3.—Renal blood flow in normal subjects and patients with chronic and acute renal failure. Renal blood flow was decreased to a comparable degree during both chronic and acute renal failure although only the patients with acute renal failure were oliguric and in need of dialysis. Only in one instance did renal blood flow increase during the recovery phase of the acute renal failure. Reproduced by permission of the publisher.¹⁷)

redistribution of renal blood flow from the cortex to the medulla during acute renal failure. These studies also provided some indirect evidence against the role of interstitial edema as a pathogenetic factor in acute renal failure. While enlargement of the kidney is frequently seen in patients with acute renal failure, 14 of 28 of their patients had no notable enlargement of the kidney, and in some instances the kidneys were larger during the diuretic phase than the oliguric phases of their acute renal failure.¹⁸ These findings indicate that although it once was suggested that interstitial edema causing collapse and obstruction of tubules might be a factor in pathogenesis of acute renal failure, it apparently is not an important one.

Currently there are three main factors which have been invoked to explain the pathogenesis of acute renal failure: (1) cessation of filtration rate due to afferent arteriolar vasoconstriction, (2) cessation of filtration rate due to tubular obstruction with casts and (3) continued filtration with "back-leak" of the filtrate through damaged tubular epithelial cells into the peritubular circulation. Several experimental models of acute renal failure have been used to study these potential factors. The three most frequently used models in rats are those in which the acute renal failure is produced by the injection of methemoglobin, mercuric chloride or glycerol. In all these models dehydration from 24 to 48 hours is necessary before injection of the substance to produce acute renal failure consistently. Figure 1 illustrates the abundance of casts in the collecting ducts of

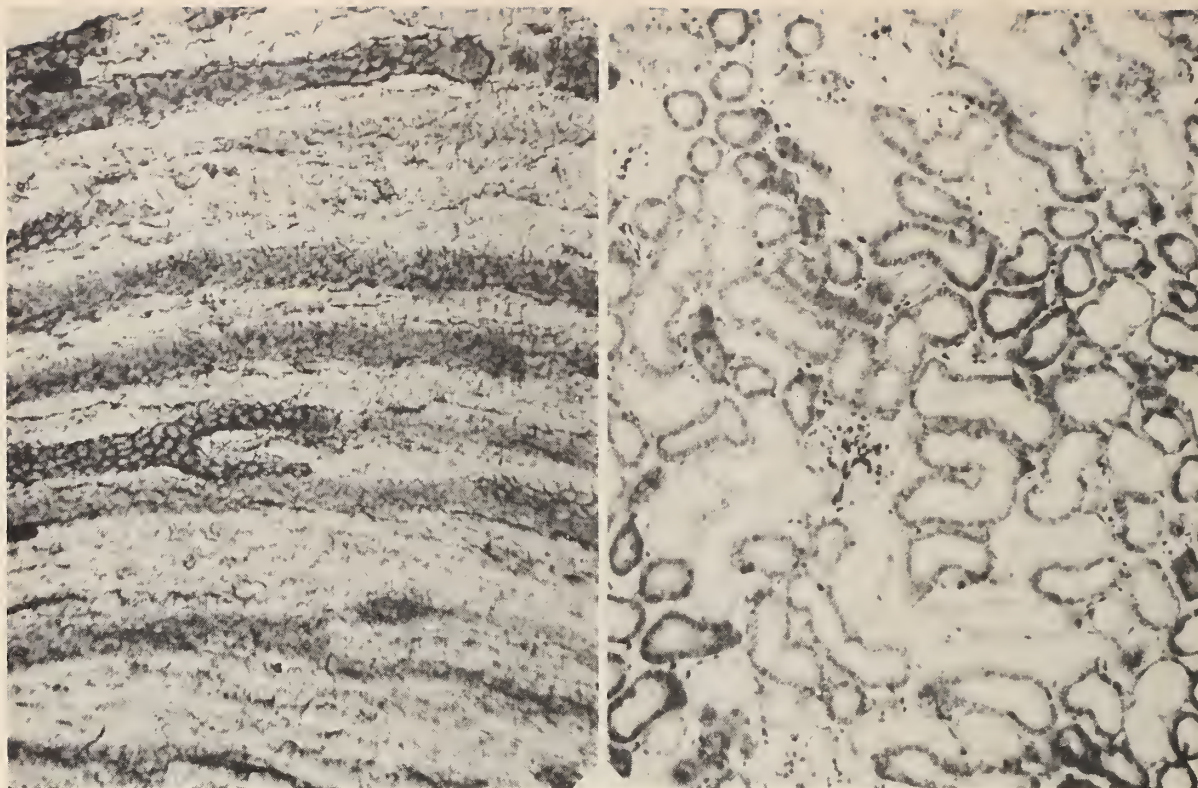


Figure 1.—Methemoglobin-induced acute renal failure in a rat. Abundance of casts in collecting ducts are shown in left frame and dilatation of proximal tubules are shown in the right. (Provided by the courtesy of W. J. Cirksena, M.D.)

a rat three hours after the injection of methemoglobin. The occurrence of such histological findings in acute renal failure constitutes one of the main reasons for belief that the cause of the acute renal failure may be obstruction. In accord with this possibility is the finding that these intraluminal casts are associated with dilatation of the more proximal aspects of the nephron as is illustrated in Figure 1. Since the histological findings were quite compatible with tubular obstruction by casts, it was very enticing to attempt to "flush out" these casts by the intravenous infusion of substances such as mannitol. Indeed, in various experimental studies acute renal failure has been prevented by the prior administration of mannitol and other colloid solutions.²⁰ In addition to the diuretic effect of these solutions, infusion of them is also associated with effects on renal hemodynamics, such as decreasing renal vascular resistance. Hence, although they may prevent acute renal failure, one then must forego knowing whether the primary pathogenic factor was obstruction or increased renal vascular resistance.

There is one study, however, that provides some support for an importance of an effect on renal vascular resistance. Ethacrynic acid is known to produce very little diuresis in rats, in contrast to its potent diuretic effect in man. Nevertheless administration of ethacrynic acid has been shown to prevent acute renal failure in rats.²¹ This finding might suggest that this drug, and perhaps other infusates such as mannitol, dextran and saline solution might prevent acute renal failure not by "flushing out" the tubule casts and relieving the obstruction, but by altering renal dynamics. Since ethacrynic acid²² and mannitol²³ are known to decrease renal vascular resistance, and if the main pathogenetic factor of the acute renal failure is ischemia rather than obstruction, the prophylactic effect of ethacrynic acid in rats could be explained by its vascular effect.

The technique of micropuncture of individual nephrons has been recently used to investigate the relative contribution of ischemia versus obstruction in the pathogenesis of the acute renal failure. The use of this technique allows the

measurement of the intratubular pressure before and after the induction of acute renal failure. If the primary cause of the oliguria is obstruction with a secondary cessation of nephron filtration, then the intratubular pressure should be increased after the induction of acute renal failure. On the other hand, if the primary cause of the cessation of filtration is vasoconstriction of the afferent arteriolar, then the intratubular pressures would be expected to be decreased after the induction of acute renal failure. Oken et al have demonstrated that intratubular pressures are decreased, not increased, after the induction of acute renal failure in rats with either the injection of glycerol (Chart 4)²⁴ or mercuric chloride.²⁵ These results have therefore been interpreted to provide evidence that renal ischemia and not obstruction is the main cause of the decrease in glomerular filtration rates and the oliguria in acute renal failure.

Studies by Jeanike et al²⁶ with the methemoglobin model of acute renal failure in rats have suggested, however, that in certain instances obstruction may be important. This investigator found that in rats dehydrated for 24 hours, the induction of acute renal failure was associated with an intratubular pressure of 22 mm of mercury in contrast to a mean intratubular pressure of 13 mm in control rats. However, if the animals were dehydrated for 48 hours, then the average intratubular pressure after induction of acute renal failure was not significantly different from that of the control group. Jeanike interpreted these data as indicating that the degree of dehydration might also indicate what pathogenetic factors are involved—that is, with 24 hours of dehydration obstruction might be the most important pathogenetic factor while after 48 hours of dehydration the primary pathogenetic factor may be constriction of the afferent arteriole.

A heterogenous population of nephrons with different intratubular pressures has also been described in experimental acute renal failure. Ruiz Guñazu et al²⁷ have reported normal intratubular pressures in non-dilated tubules and increased intratubular pressures in dilated tubules of rats in which acute renal failure has been induced by the injection of methemoglobin. These same workers²⁷ have also measured pressures in the efferent arteriole before and after the induction of experimental acute renal failure in an effort to

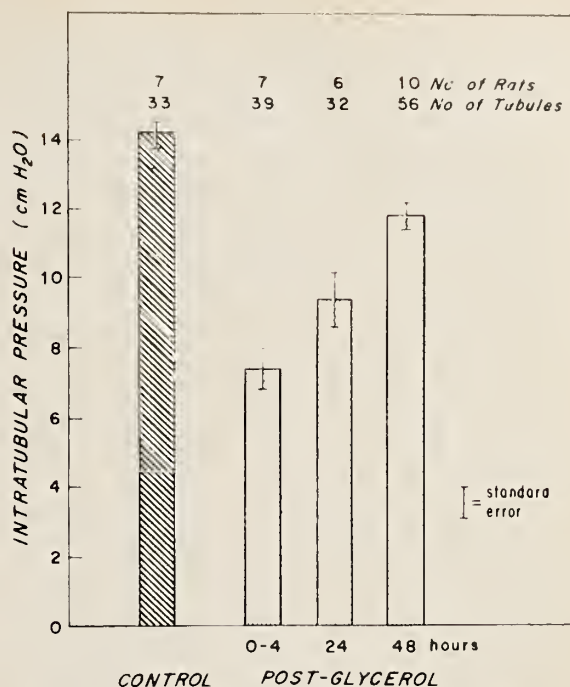


Chart 4.—Intratubular pressure measurements in rats with glycerol-induced acute renal failure. The post-glycerol injection pressures are all significantly lower than the control pressures. (Reproduced by permission of the publisher.³³)

assess whether the decrease in filtration rate is due primarily to an increase in constriction of the afferent arteriole or to a dilatation of the efferent arteriole. With constriction of the afferent arteriole a decrease in pressure in both the tubule and efferent arteriole would be expected, while dilatation of the efferent arteriole would be associated with a decreased pressure in the tubule but not the efferent arteriole. These investigators found a progressive fall in pressure in both the efferent arteriole and the tubule during the first six hours after the injection of methemoglobin. This observation suggested that the primary factor in the occurrence of the acute renal failure was vasoconstriction of the afferent arteriole.

There is very little information available concerning the mediator of such constriction of the afferent arteriole. Thurau²⁸ has suggested that the renin-angiotensin system may be involved. With his associates he has reported experimental evidence that an increase in intraluminal sodium concentration at the distal nephron site adjacent to the *macula densa* is associated with a collapse of the proximal tubule, presumably as a result of cessation of filtration. He has suggested that the mediator of this effect of increased luminal,

and presumably intracellular, sodium concentration is an increase in renin and subsequently angiotensin activity. On the background of this information he has conjectured that the luminal sodium concentration adjacent to the *macula densa* may increase in acute renal failure and thereby activate the renin-angiotensin system. The increase in angiotensin activity would in turn cause constriction of the afferent arteriole and cessation of filtration. Since dehydration is known both to increase renin activity and to predispose to acute renal failure,²⁹⁻³⁰ such a hypothesis was not unreasonable and, in fact, renin activity has been shown to be increased in several varieties of acute renal failure.³¹⁻³²

The increase in antidiuretic hormone activity and the concentrated urine associated with dehydration have been found not to be necessary components for the occurrence of acute renal failure, since the experimental induction of acute renal failure has been produced in animals with diabetes insipidus.³³ Chronic saline loading has been shown to prevent the occurrence of acute renal failure and is also known to suppress renin activity.³⁴ There are, however, several difficulties with the hypothesis that increased activity of the renin-angiotensin system is the primary factor in the pathogenesis of acute renal failure. Patients with renal vascular hypertension and malignant hypertension have increased renin levels without acute renal failure. Moreover, Oken and associates³⁵ recently demonstrated that experimental acute renal failure cannot be prevented by prior treatment with anti-renin antibodies. Thus, factors other than (or in addition to) increased activity of the renin-angiotensin system would seem to be involved in the pathogenesis of acute renal failure.

There is some experimental evidence which suggests that "back-leak" of filtrate rather than cessation of filtration is involved. Bank et al³⁶ measured the inulin concentration in the tubular fluid along the nephron in rats with experimental acute renal failure due to mercuric chloride administration. In normal circumstances the concentration of inulin increases progressively along the length of the nephron, since fluid is reabsorbed and inulin is a non-reabsorbable substance. However, in rats with acute renal failure the concentration of inulin in the proximal and distal tubule was not found to be different although the volume of fluid in the distal tubule

was much lower than in the proximal tubule. Bank and his co-workers therefore suggested that, due to the damaged tubular epithelium, inulin was "leaking" from the tubular fluid to peritubular blood along with the movement of water and solutes in the same direction. These same investigators also injected lissamine green into these rats and observed that the substance then could be seen in the proximal but not the distal tubule. Since lissamine green, like inulin, is not normally reabsorbed, this finding further supported their hypothesis of increased "back-leak" of filtrate from lumen to blood in acute renal failure. Other investigators³⁷ provided similar evidence in experimental acute renal failure. This evidence, however, has been primarily obtained in models of acute renal failure induced by the administration of nephrotoxins such as mercuric chloride.³⁶⁻³⁷ In these models of acute renal failure the tubular epithelium may be completely necrosed and denuded with only basement membrane remaining; thus such a "back-leak" of filtrate is reasonable.³⁸ However, since this severity of tubular epithelial damage is virtually never seen in acute renal failure in patients, even in association with the ingestion of nephrotoxins, the importance of this factor in the pathogenesis of acute renal failure in patients remains in question.

The primary factors in the pathogenesis of acute renal failure would thus seem to be constriction of the afferent arteriole and obstruction to tubular flow by cast formation. The results of a very interesting recent study allows for the integration of these two factors. Oken and associates³⁸ demonstrated that if the pressure in the tubular lumen in animals with acute renal failure is increased to a level expected in normal rats that the intraluminal casts are dislodged and the filtration rate in that nephron returns to a near normal level. In this context the initiating event could be the constriction of the afferent arteriole which leads to a decrease in filtration rate and a slower tubular flow rate. In the presence of this diminished tubular pressure and flow rate, sludging of debris and formation of casts may occur. These materials ultimately may lodge in the collecting ducts and lead to obstruction with persistence of oliguria. While such obstructive casts may only occur as a result of the constriction of the afferent arteriole and decreased intratubular pressure, their presence may contribute to the

persistence of the acute renal failure and in their absence the onset of the diuretic phase might occur much sooner.

In summary, acute renal failure may occur in a variety of clinical circumstances and the clinical diagnosis must depend in large part on the exclusion of both prerenal and postrenal causes of oliguria. Analysis of the composition of urine may be very critical in this regard. The frequency of dialysis and the choice between peritoneal and hemodialysis should be based primarily on the ability to treat and prevent the occurrence of urmic symptoms. Although a full understanding of the pathogenesis of acute renal failure will require more investigation, current evidence in experimental animals suggests that both constriction of the afferent arteriole and obstruction of tubular flow by intraluminal casts may be important.

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The Doctor and the "Doper"

J. THOMAS UNGERLEIDER, M.D., *Los Angeles*

THERE ARE WAYS to make it simpler for the physician to deal with the problems of drug abuse and to help him make the decision to become involved with the treatment of drug abusers in the first place.

What is the role of the physician treating adolescents who come to him with a drug problem?

The Doctor as an Educator

Part of drug abuse prevention, by physicians, is through the education of their patients. The goal is to provide information to youth about the risk factor involved in the use of the various kinds of drugs available today.

Much of the available information is mixed with myth, and one hears and reads all kinds of unproven and dangerously false "facts" about the illegal use of drugs. The physician is in an ideal position to provide his young patients with factual, unbiased information. Naturally he should carefully evaluate the credibility of any printed information he passes out. (See the appended special bibliography on drug abuse.)

The Doctor as a Model

The physician is still one of the most esteemed of adults to young people, and today's youths are desperately trying to identify with adults. But they want to find adults who are neither "square" nor themselves drug abusers. This is what much of their testing and probing questions for the doc-

tor is designed to serve. The physician should not be misled when the young drug user does not approach him with the traditional, "O wise physician, tell me about the harm of marijuana," but rather says something like, "Alcohol is worse than pot," then sticks out his chin and waits. What they often get is a lecture on morality, which they invariably "tune out." What they need is an admission on the part of the doctor that one drug is not inherently *good* (from a moral standpoint) while another drug is *bad*. Chemicals have effects and side effects. That is what can be taught.

The Importance of Honesty

Scrupulous honesty with these young people is vital. Youth respects a straightforward, "We just don't know." The decision as to any kind of risk-taking behavior—here the risk involved in using drugs—is a very personal one which will be made by each youngster himself. It is to be hoped that the physician will be the one to impart the risk-factor information (when it is known) to provide some factual basis for such decisions.

What are some of the requirements which one must have in order to be effective with young people?

Obviously the physician must like youngsters if he is to successfully treat them. Not every one does. In fact many adults are completely "turned off" and threatened by the long hair and "psychedelic" clothing fads of today's youth. If the physician feels this way, to the point of lumping all

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"mod-looking kids" into the category of drug abusers, then he will do himself and his patient a favor to refer the youngster on to someone who is comfortable with young people. On the other hand the physician, to be effective, must realize that young people are not looking for another peer or "fellow hippy" when they confide in their doctor. The physician must be neither a drug missionary nor a drug moralist.

The physician must not be so committed to the concepts either of personal freedom or of obedience to authority that he misses the clues as to what the youngster is seeking. The need may be for more parental interest and giving of responsibility and privileges, or it may be for more parental control and less permissiveness.

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Certain clues can help toward diagnosis.

- Drug abuse is a symptom, a piece of behavior, that must be scrutinized.

- A vital differentiation is that of *drug use* from *drug abuse*. Drug use is usually defined as that form of drug-taking which interferes with neither a patient's intrapsychic equilibrium nor his social effectiveness on the job, in daily life and in relationships with other people.

- One obviously needs to know what drugs are being used. Many of the drugs sold "on the street" do not contain what they purport to contain. Hence a careful history is of great importance.

- The route of administration is important; parenteral use of any medication is more serious prognostically than ingestion.

- The *pattern* of drug use must be ascertained: Does the patient use drugs in the morning before school, all day long, or "just" on weekends? Is the use continuous or in sprees? Is it to alleviate depression, avoid responsibilities, alert significant adults to the problem, or is it in lieu of relationships? Is it to get a delirious reaction (as with barbiturates) or to increase sensory bombardment (as with psychedelics). And, if the latter, is it to find happiness and pleasure or a new religious way of life? Is the life style altered consistent with the type of goal?

- One must obtain a detailed history as to concomitant legal problems including recent arrests or probation. It is important to find out exactly who in the environment knows what about each

of the patient's drug behaviors. In other words, what specifically do the parents, school counselors, friends and the like know? When these details are elicited it will usually become obvious whether there is drug use or abuse. It is also important to ascertain through the history whether or not there is impairment of function at work, at school, while driving, or in relationships.

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There are useful guidelines that can be followed in treatment.

- If the doctor determines that the young patient is using drugs rather than abusing them, then it is his responsibility to ascertain that the patient is aware of the possible legal consequences of his behavior and that he has some feedback mechanisms (observing ego) so that if he later becomes impaired as to functioning he will consider the role of the drugs. The doctor must decide whether to tell the youngster's parents. Is he violating a privileged communication or does the youngster want the parents informed? One purpose in telling them is to alleviate their anxiety and enable them to recognize the problem and then to intervene effectively. Very frequently just the setting of parental limits and expression of interest will be all the youngster needs to stop his drug experimentation. But the parent, if all intervention fails, also has the right ultimately to refuse to put up with the teenager's drug use while the youngster lives at home. Leaving home may have to involve another facility if the teenager is young. But if he is older (19 or 20) it may just involve insistence upon his moving out to "make it on his own."

- It is more difficult for any physician to ascertain the cause of the drug use than it is to determine whether it has progressed into drug abuse. When it has become abuse and when simple confrontation and involvement of parents does not greatly alter the situation, then further steps are indicated. With loss of functioning at school, at work, while driving or the like, the parent must be helped to step in, place firm controls on the youngster and arrange for professional help. In fact, the physician will often be consulted only after the patient has been arrested. Then the question about which he is consulted is one of deciding between probation with psychiatric care, and a forestry or youth camp. It should be borne in

mind that some young people do need an environment where they can grow up drug-free for a time. Some of the younger teenagers who are heavily into drugs do very well at some of the forestry camps that the state and county maintain.

- The physician must help dispel the prevalent idea today that if you say no to your child you do not love him.

- If a drug-induced psychosis or schizophrenic reaction concomitant with the use of drugs is detected, then admittance to hospital is indicated. A stay in hospital is also indicated for withdrawal of physiological addiction to barbiturates (particularly secobarbital or "reds"). The withdrawal for these must be gradual, and as an inpatient, to avoid seizures.

- If the patient is taking heroin the physician should be aware of the new methadone maintenance programs which are recent additions to our therapeutic armamentarium in California. Requirements for acceptance into this type of treatment program usually include that the patient be an older, confirmed heroin user who has failed in other kinds of treatment.

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As adult citizens and as physicians we must assume responsibilities in dealing with drug abuse. We are in a unique position to make a vital contribution toward solving this serious health problem if we will but become involved.

BIBLIOGRAPHY

The following is a drug bibliography which the college and high school students working with Project DARE (Drug Abuse Research and Education) have evaluated and found helpful in their work.

For a complete list of drug literature which has been evaluated and is recommended by the Project DARE student evaluation team write to Project DARE, The Neuropsychiatric Institute, UCLA Center for Health Sciences, 760 Westwood Plaza, Los Angeles, Ca. 90024

1. Recent Research on Narcotics, LSD, Marihuana and Other Dangerous Drugs—Public Health Service Publication No. 1961, National Institute of Mental Health, 5454 Wisconsin Avenue, Chevy Chase, Md. 20015

2. What You Should Know About Drugs and Narcotics—Alton Blakeslee—Contact the Associated Press for copies

3. Damaging Effects of Drug Abuse—The California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102

4. Thinking About Using Pot—The San Francisco Psychiatric Medical Clinic, 2633 East 27th Street, Oakland, Ca. 94601

5. Hallucinogenic Agents—A Concise Review—Schering Corporation, Bloomfield, N.J. 07003

6. Some Questions and Answers—Series on Marijuana, Barbiturates, Amphetamines, LSD—From: The National Institute of Mental Health, 5454 Wisconsin Ave., Chevy Chase, Md. 20015

7. Facts About (Series) Tranquilizers, Amphetamines, Barbiturates, Solvents, LSD, Marijuana—Drug Abuse Education Unit, Food and Drug Directorate, 33 Russell Street, Toronto, Canada

8. Adolescence for Adults—Blue Cross of Southern California, 4777 Sunset Blvd., Los Angeles, Ca. 90027

9. Before Your Kid Tries Drugs—National Institute of Mental Health, 5454 Wisconsin Avenue, Chevy Chase, Md. 20015

THE CHILD WHO ROCKS YOU AWAKE

How do you stop a child's rocking in bed at night and keeping the whole family awake?

"Some children get a tremendous response from head banging or rocking the bed. This is the kind of thing that makes them feel comfortable. I don't think there's anything really wrong with it up to the age of two. Past that age you do have to worry and you should evaluate for possible central nervous system problems or mental retardation—particularly if the rocking is violent and you can't reason with the child. Many children with a central nervous system disorder or mental retardation are head bangers.

"For the most part the practical therapy involves trying to get the family to accept this habit, maybe using cotton in their ears at night to cut out the noise. The bed could also be padded or placed in the middle of the room with blocks on it so it won't hit the walls. . . .

"Another thing: sometimes these children seem to respond pretty well to Benadryl® given at night. . . . I usually start them out on 10 mg and build up to maybe 30 or 40 mg, depending on how they do."

—J. WARD STACKPOLE, M.D., Burlington
Extracted from *Audio-Digest Pediatrics*, Vol. 15, No. 24, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057

Important Advances in Clinical Medicine

Epitomes of Progress -- Psychiatry and Neurology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Psychiatry and Neurology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Psychiatry and Neurology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panels to the Section on Psychiatry and Neurology of the California Medical Association and the summaries were prepared under their direction. (Members of the Panel are listed on page 54.)

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

Psychiatry

Current Use of Lithium Carbonate

IN RECENT YEARS, LITHIUM, now available as the carbonate for general prescription, has proved to be a valuable addition to the psychotropic drug armamentarium. It is particularly effective in rapidly curtailing the manic phase of manic-depressive illness, and is also generally agreed to be prophylactic against the recurrence of mania when given in maintenance dosage. Whether or not it has an anti-depressant effect is as yet a matter of controversy.

The candidate for lithium therapy must be screened for cardiac or renal impairment. Because of a relatively narrow therapeutic-toxic margin, care must be taken to maintain the serum lithium level below 2.0 mEq per liter. Once the dosage regimen is stabilized, however, less frequent serum lithium determinations are required, and significant central nervous system toxicity may be avoided by clinical alertness alone, since there are prodromata of drowsiness, coarse tremor, anorexia and slurred speech.

JOHN A. TRIBBEY, M.D.

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School Phobia: Controlled Imipramine Treatment

THE CHILDREN AND FAMILIES of 35 school phobic children between the ages of 6 and 14 received a multi-discipline treatment program, concurrently with imipramine or placebo treatment over a six-week period. Among children treated with imipramine, 81 percent returned to school against 47 percent of those treated with placebo ($P < .05$). All of the imipramine-treated children reported feeling much better, whereas 21 percent of the placebo-treated group reported similar improvement after six weeks ($P < .005$). Imipramine doses ranged from 100 to 200 mg per day.

Imipramine effects could not be detected after three weeks of therapy, but were clearly present after six weeks. Of ten items rated by the psychiatrists, four reflecting the severity of the child's phobic behavior—the child's venturesomeness from the mother, physical symptoms while going to school, and fear of going to school—were significantly improved by imipramine.

Among ten items rated by mothers, only one of ten reflecting depressive mood showed a significant drug effect. On the whole, side effects were not significant.

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DONALD F. KLEIN, M.D.

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Gittelman-Klein R, Klein DF: Controlled imipramine treatment of school phobia. *Arch Gen Psychiatry*, in press

Abortion—Psychiatric Implication

THERAPEUTIC ABORTIONS HAVE become a prominent social, legal, and medical issue in the past three years, with many rapid changes in all three areas. Psychiatry is dynamically involved in all these areas.

In California in 1968, the first year under the new Abortion Law, there were 5,031 therapeutic

abortions done, 87.6 percent for mental health reasons. In 1970, the comparable figures are 62,672 and 98.2 percent.

The California Medical Association and the American Psychiatric Association are on record for a more liberalized law, namely that the question of a therapeutic abortion be a matter between the patient and her doctor. In the California Medical Association there continues much controversy seeking solutions to the problem of unwanted pregnancies.

The psychiatric consultation for therapeutic abortions has embraced many new problems during this period. Such questions as should the psychiatric consultation be directed toward seeking psychiatric justification for abortions or establishing psychiatric indications? Even though the law does not specifically require such, most hospital therapeutic abortion committees still require a psychiatric consultation.

An unwanted pregnancy is a crisis situation, often requiring psychiatric treatment. The degree of psychiatric involvement is a clinical judgment of the psychiatrist as in other crisis work. The abortion itself, managed without increasing the anxiety and guilt of the patient and providing opportunity for her to activate healthy defenses, can be a truly therapeutic experience. For example, psychological growth in a teenager often is seen as she overcomes her fear of sharing her emotional problems precipitated by an unwanted pregnancy with her parents.

The long-range effect of a therapeutic abortion on the psychological life of a woman is poorly defined. Collecting reliable data on the subject has many frustrations, accounting for the paucity and incompleteness of such studies.

The evolving psychiatric opinion seems to be that with proper psychiatric care during the time of the crisis there is little damage. However, less stable personalities and poor management may precipitate more serious psychiatric problems. There are indications that more serious psychological damage may be present in those women for whom the therapeutic abortion has been denied.

GEORGE A. GROSS, M.D.

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Senay E: Therapeutic abortion—Clinical aspects. *Arch Gen Psychiatry* 23:408-415, Jul-Dec 1970

The Hyperactive Child

RECENT STUDIES INDICATE that the primary symptom in hyperactive children is most frequently a shortened attention span. Hyperkinesis, *per se*, is one of the secondary symptoms. The so-called paradoxical "calming" effect of psychostimulants on such children appears to be the result of increasing the attention span. Secondary symptoms, including hyperkinesis, impulsivity, aggressivity and depression, usually improve when the underlying deficit in the attention span has been corrected.

The long-term prognosis for untreated severe cases is poor because of repeated academic failure and the development of severe personality disorders. Early intervention with parental counseling, special educational techniques and pharmacotherapy are indicated. Methylphenidate (20 to 60 mg per day) and imipramine (50 to 100 mg per day) appear to be the most efficacious medications currently available. Pharmacotherapy must often be continued until early puberty when the children have usually developed alternative means to focus their attention.

LAWRENCE M. GREENBERG, M.D.

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Werry JS: Developmental hyperactivity. *Pediatr Clin North Am* 15:581-599, Aug 1968

Sex Education in Medicine

SEX EDUCATION IS NOW required in five and is elective in fifty United States medical schools. Relevant topics include anatomy and physiology of normative sexual behavior, sexual variants (for example, homosexuality), sexual problems and symptoms (impotence, frigidity), sex education and counseling, and cultural dimensions.

Most courses have the dual goals of increasing knowledge and resensitizing attitudes in students so that they become more comfortable, objective,

and understanding of sexual behavior in their patients.

At UC Davis School of Medicine, our course titled "Medical Aspects of Human Sexuality" follows the above principles. All sessions are jointly conducted by a male psychiatrist and a female gynecologist. Participating specialties include adult psychiatry, child psychiatry, pediatrics, obstetrics and gynecology, and urology. Teaching sessions use films, videotapes, live patients, panels, and occasional lectures.

Sex education in medicine reflects the profession's growing awareness of patients' needs and of new techniques of treatment. It is appropriate for both students and practitioners, since physicians are called upon more and more to deal with patients as integral human beings whose health is multidimensional.

PAUL R. MILLER, M.D.

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Vincent CE (Ed): *Human Sexuality in Medical Education and Practice*. Springfield, Illinois, Charles C Thomas, 1968

Alcoholism: Contemporary Attitudes

IT HAS BEEN ESTIMATED that there are nine million alcoholics and problem drinkers in the United States today, a vast problem of suffering and psychiatric trauma for 36 million family members. Alcoholism has been called the most serious medical health problem of 1970. In keeping with this, Congress passed an act in 1970 which established the National Institute on Alcohol Abuse and Alcoholism whose immediate objective is to make treatment and rehabilitation services available and whose long range plans are to develop effective practical means of prevention of alcoholism.

A recently published survey of Veterans Administration psychiatrists and psychologists reveals that they share a decided inconsistency in their attitudes on alcoholism and have only limited interest in treating hospitalized alcoholics. While rejecting the disease concept, these workers prefer to characterize alcoholism as a behavior problem. In the face of such reluctance to treat alcoholics, it has been suggested that the already over-loaded general hospitals be spared

the alcoholic patient and that most work on the problem take place in programs allied with industry as well as within the mental hospital setting. Additional experimental work might be done through consultations to the jail system providing therapy and treatment during protective custody.

S. LAWRENCE POMER, M.D.

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Knox WJ: Attitudes of psychiatrists and psychologists toward alcoholism. *Am J Psychiatry* 127:1675-1679, Jun 1971

Electrosleep Therapy: Current Usage in Psychiatry

ELECTROSLEEP THERAPY has been in extensive clinical use for a variety of psychiatric syndromes during the past 20 years in Russia and Central Europe. Few double-blind, controlled studies were done and therapeutic efficacy has been difficult to evaluate. From recent controlled studies it is highly suggestive that this safe and simple means of treatment is effective for chronic anxiety, tensional states with associated insomnia.

Treatments usually last 30 minutes and consist of a low voltage, pulsating direct current administered from an Electrosone® 50 unit via electrodes over the eyes and mastoid processes. The average course of treatments varies from five to ten given over a period of two or three weeks. Some patients may require maintenance treatments given at varying intervals as determined by recurrence of symptoms. Side effects are minimal with no known absolute contraindications except that some patients with primary depressive disease may decompensate and become actively suicidal. Thus, electrosleep therapy should not be the treatment of choice in this disorder and should be used with caution if this diagnosis is suspected.

JOHN P. FEIGHNER, M.D.

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Rosenthal SH, Wulfsohn NL: Electrosleep—A clinical trial. *Am J Psychiatry* 127:533-534, Oct 1970
Feighner JP, Brown SL, Olivier JE: Electrosleep therapy—A controlled double blind study. *In press*

Biofeedback Training in Voluntary Control of EEG Alpha Rhythms

INDIVIDUALS CAN BE trained to increase or decrease the percent time of alpha in their electroencephalogram by a technique of providing the subject with a tone that varies in loudness or pitch exactly as the amplitude of the alpha rhythm varies. The subject is told to explore the relationship between various states of mind and the variations in the tone, and that he should try to find those states of mind that keep the tone loud or quiet.

The high amplitude alpha state appears to be associated with quiet, alert, calm states of consciousness. The applicability of this technique in psychiatric treatment is being considered.

JOE KAMIYA, PH.D.

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- Tart C (Ed): Operant control of the EEG alpha rhythm and some of its reported effects on consciousness, *In* *Altered States of Consciousness*. New York, Wiley, 1969

The Psychophysiology of Sleep

CONTINUOUS NOCTURNAL MONITORING of electroencephalogram, eye movement and other variables has considerably extended our knowledge of the psychophysiology of sleep. The sleep EEG shows greater change with age than does any other measure of brain function. These changes may prove of clinical (diagnostic) value during the earliest months of life and in the normal and senile aged. Also of direct clinical relevance are the findings in narcolepsy; for many patients, the narcoleptic attack is an attack of rapid eye movement (REM) sleep. Drugs which are effective in delaying the onset of (amphetamines) or of suppressing (tricyclic antidepressants) REM sleep are of value in treating some aspects of the narcoleptic syndromes. The autonomic instability of REM sleep has led several investigators to speculate that REM processes may contribute to cardiovascular disorders in susceptible patients. The

data thus far are inconclusive. In some cases of delirium tremens there are extremely high values of REM sleep and it seems possible that aberrant REM mechanisms may play a role in the symptoms of this condition. Thus far, different classes of psychoactive drugs appear to exert different patterns of effects in the sleep EEG; if confirmed by further investigation, these findings may provide a clue to the mechanisms of drug actions. However, it is clearly premature to make a drug choice (for example, among hypnotics or tranquilizers) on the basis of reported effects on the sleep EEG, since the functional significance of these effects remains unknown. Equally unknown are the biological functions subserved by either REM or slow wave sleep. In the former, brain activity appears increased above waking levels, and in the latter this activity is at least equal to that of the waking state. Thus, the traditional view that sleep provides rest—through inactivity—for the brain is clearly wrong. The search for an understanding of the functional significance of sleep has become a leading cause of insomnia among workers in several fields of neurobiology.

IRWIN FEINBERG, M.D.

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Megavitamins in Schizophrenia

VITAMINS IN MEGA DOSES have recently been proposed as therapeutic agents for an array of disorders. Similar claims have been presented for these agents in the treatment of schizophrenia. Hoffer and Osmond have reported that nicotinic acid in high doses (at least 3000 mg per day) had a beneficial effect in schizophrenia with virtually no toxicity. This claim was not based on control study data and has subsequently not been confirmed by several large scale studies in Canada.

In 1966 Hoffer and Osmond suggested that another related compound, nicotinamide adenine dinucleotide (NAD) was more effective in treating schizophrenia, again based on uncontrolled observations. Subsequently several studies carried out in chronic schizophrenics here again failed to substantiate these claims. Therefore we

undertook a double blind controlled study in acute hospitalized schizophrenics comparing NAD with chlorpromazine. The ten patients assigned to chlorpromazine were given a maximum dose of 1200 mg per day and attained the following responses: marked or moderate improvement, 4; minimal, 4; no change, 2; and none worse. Of the 13 assigned to NAD and given a maximum dose of 3 grams per day, 4 became worse, 3 had no change, 4 had minimal improvement, and 2 either moderate or marked improvement.

Thus it may be concluded that there is considerable discrepancy between the claims reported by enthusiasts with NAD from uncontrolled studies and the findings derived from controlled studies.

SAMUEL GERSON, M.D.

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Meltzer H, Shader R, Greenspoon L: The behavioral effects of NAD in chronic schizophrenia. *Psychopharmacologia* 15:144-152, 1969

The Second Year of Life

THE OBSERVER SEES MANY signs of the high order of changes taking place in the second year of life. These occur in the motor, cognitive and affective spheres of behavior: There is the increasing confidence and mastery of locomotion, the rapid increase in vocabulary and verbal discourse, and development of the capacity to use the word "no," an achievement, according to Spitz, of a higher integration in the unfolding personality of the child.

Piaget reports shifts in cognitive functioning. This now includes an inner world of objects, animate and inanimate, which exist in the child's mind even when not directly perceived and acted upon. His sense of self, coincident with a sense of body scheme, becomes more fixed. All this occurs within the affective matrix of the mother-child relationship.

By the second year of life, the processes of separation and individuation, the "second hatching" from mother, are well under way. Mahler and her coworkers have carefully described sub-phases in this process. These are practice, rapprochement and individuation. Practice is seen in the child's increasing ability to leave his

mother as he gradually develops confidence in his retention of mental representations of his mother. This also coincides with the spurt in locomotion and exploration in the first half of the second year. Rapprochement in his turning back to her from his feeling that he has overextended his independent forays. This is around 16 to 18 months. Continued individuation, that is, increasing mastery of many activities, follows on the base of a good rapprochement and the ever firmer sense of self and "inner-remembered-mother-emotionally-available-as-needed."

Two common examples where mother is emotionally unavailable are during prolonged physical separation or when mother is depressed. The result is an increased unresolved anxiety about separation often signaled by behavioral signs and symptoms. There is interference with the forward developmental progress of the child. When this persists, it warrants psychiatric intervention.

JOSEPH AFTERMAN, M.D.

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Recent Developments in the Prevention of Mental Retardation

THE PREVENTION OF MENTAL retardation is a major research concern. Federal legislation provided funds for the development of mental retardation centers throughout the country. Many of these centers are now operational. Recent advances have developed in primary, secondary, and tertiary prevention. In primary prevention some of the new developments are:

- Maternal malnutrition has significant effects on intrauterine brain growth, particularly the cerebrum.¹ The effects are partially reversible, as noted by some investigators,² by adequate post-natal nutrition (which further emphasizes the need for good prenatal and infant care based on understanding of the needs of pregnant women and the fetus.

- Proper genetic counseling has reduced inheritable conditions.³
- Rubella and measles immunization.⁴
- PKU testing.
- The diagnosis of inborn errors of metabolism and chromosomal abnormalities through amniocentesis.⁵

- Lead poisoning prevention by recently adopted federal legislation to prevent the use of lead-containing interior paints.

New developments in secondary prevention are:

- Familial mental retardation, usually associated with deprivation and poverty is being influenced by psycho-social interventions (direct effectiveness is not only related to clinical interventions but depends upon massive community efforts to correct social ills).⁶

- Early case-findings and screening.
- Counseling with families.⁷

In tertiary prevention:

- Amelioration is best achieved by special classes and schooling, and vocational rehabilitation through direct employment and sheltered workshops.

- The provision of clinical services, medical and psychiatric, for retarded children and their families has improved performance.⁸

- It has been demonstrated that institutionalized mildly retarded children adopted into homes that provide for their physical and emotional needs show improved learning abilities and as adults achieve higher levels than institutionalized controls or would have been predicted by the intellectual, economic, social or vocational levels of their biological parents.⁹

IRVING PHILLIPS, M.D.

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Cerebral Evoked Potentials in Schizophrenia

COMPUTER ANALYSIS OF electroencephalographic (EEG) responses to repeated stimuli yields information not ordinarily available in the usual clinical EEG. Thus, such evoked potentials (EPs) are used to test simple sensory competence (for example, EP audiometry). However, EPs also reflect more subtle cognitive processes. Schizophrenia is characterized by a variability of cognitive functioning as manifested, for example, by disorderly thought processes. This excessive cognitive variability is reflected in an excessive EP variability. High EP variability is no more unique to schizophrenia than is cognitive variability—both are also found in children and in Korsakoff's psychosis. Cognitive instability can usually be assessed adequately by interview. However, when language fails—as for example, because of cultural differences, language barriers or mendacity, EP variability can provide evidence on cognitive function.

ENOCH CALLAWAY, M.D.

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Jones RT, Callaway E: Auditory evoked responses in schizophrenia—A reassessment. *Biol Psychiatry* 2:291-298, Jul 1970

Narcolepsy and Cataplexy—Innovations in Diagnosis

THE PRIMARY PATHOLOGICAL process in narcolepsy is the attack of sleep. Just as there are two kinds of normal sleep, rapid eye movement (REM) and nonrapid eye movement (NREM), so do there appear to be two kinds of narcolepsy. In one, the abnormal process is sudden overwhelming attacks of REM sleep, and in the other, the abnormality is attacks of NREM sleep. It is difficult, on the basis of history alone, to distinguish between the two. However, if one or all of the auxiliary symptoms of cataplexy, sleep paralysis, and hypnagogic hallucinations are

present, the presumptive diagnosis would be REM-type narcolepsy. It is important to confirm this impression with a polygraphic recording which necessarily includes electro-oculogram, and electromyogram properly recorded, in addition to the EEG.

An attack of REM sleep or a sleep onset REM period associated with the characteristic EMG suppression, rapid eye movements, and saw-tooth waves in the EEG, in other words, a period of REM sleep exactly like that occurring normally at night, establishes the diagnosis. There are a number of dissociative processes in REM-type narcolepsy. The physiological components which ordinarily occur together in normal REM periods may occur in isolation, thus, the motor inhibitory component of REM sleep in isolation is cataplexy. The dream component of REM sleep in isolation is the hypnagogic hallucination. In the Stanford University Sleep Disorders Clinic we have seen only two patients who had the presumptive diagnosis of NREM narcolepsy. In one case, the diagnosis was changed when sleep onset REM periods developed following withdrawal from amphetamines. In the other case, the sleep attacks disappeared following withdrawal from methylphenidate. It is our opinion that a number of instances of NREM narcolepsy are in reality a drug dependency hypersomnia. Thus, REM narcolepsy may eventually develop into NREM narcolepsy due to the development of dependency on these stimulating drugs, plus their tendency to suppress REM sleep.

Treatment of REM-type narcolepsy should begin conservatively with attention to nocturnal sleep and daytime naps, if possible, and use of methylphenidate and amphetamines. Other drugs which act primarily on the motor inhibitory process are the tricyclic antidepressants, and the monoamine oxidase inhibitors. Nardil® appears to be the most easily tolerated of the latter. A combination of tricyclic antidepressants with a regimen of naps will sometimes control narcolepsy so that amphetamines do not have to be employed.

W. DEMENT, M.D.

V. ZARCONE, M.D.

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Yoss R: Treatment of narcolepsy. *Mod Treatm* 6:1263-1274, Nov 1969

Contemporary Psychoanalysis

CONTRARY TO A STILL prevailing mythology which depicts the psychoanalyst as an ivory tower isolate, the American psychoanalyst is less inclined in recent years to devote his full time to the practice of psychoanalysis. More often he is also involved in any number of activities: You will find accredited psychoanalysts teaching in medical schools and residency programs and serving as consultants in social work agencies and school health programs. They can be found observing infants and nursery school children, treating psychotics in hospitals, engaged in group therapy and deeply involved in social and community psychiatry. Scratch a consultant to any city, county, state or Federal social agency and you may find a psychoanalyst. What can be readily seen is a closer working relationship with clinical psychiatry as well as the application of psychoanalysis to the rest of the humanities.

Predictions have been made that future psychoanalysts and psychiatrists will be engaged almost entirely in coordinating, supervising and educational activities with very little time available to do therapy. Psychoanalytic therapy might then be reserved almost entirely for the professional.

Psychoanalysis is experiencing a host of professional, political and social conflicts which are affecting many organizations today. For example, the problems of the Psychoanalytic Training Institutes include: the question of affiliation with a university or medical school, methods of applicant selection and prediction and disagreement in matters of theory and technique.

Psychoanalysis is an investigative method, a psychotherapeutic technique and a collection of data and theory. That there is a lessening of new "couch research" is accepted but this has been countered by research in other fields, especially those of developmental psychology, sociology, anthropology, law, history and other behavioral sciences. Few in the field doubt that one day psychoanalysis and brain neurophysiology will be bridged. Meanwhile human phantasy and

emotions will continue to require psychic measures to deal with psychic ills.

Psychoanalysis remains in the service of those who seek to defend man from the current lethal de-humanizing effects of the machine.

S. LAWRENCE POMER, M.D.

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Rangell L: Psychoanalysis and neuropsychiatry—A look at their interface. *Am J Psychiatry* 127:125-131, Aug 1970

Evoked Cortical Potentials in Hyperkinetic Children

AUDITORY EVOKED CORTICAL potentials were studied in a group of 31 hyperactive children and in 21 normal control subjects matched for age, sex and I.Q. Most hyperkinetic children were found to have abnormally low amplitudes of auditory evoked potentials.

In hyperactive children large amplitude evoked potentials and lots of slow wave activity in the resting EEG predicted a good clinical response to stimulant medication.

Increased slow wave activity and large amplitude evoked potentials can be interpreted as an index of low cortical excitability. Reduction in both of these measures in response to stimulant medication supports this theory. Stimulant medications thus seem to act as stimulants, resulting in more cortical inhibitory control enabling the child to be behaviorally in better control of both motor output and sensory input.

There are few neurophysiological correlates of the hyperkinetic child syndrome. These techniques may assist in delination of the syndrome and help select the proper mode of treatment for the disorder.

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Satterfield JH, Dawson ME: Electrodermal correlates of hyperactivity in children, *Psychophysiology*, in press

Neurology

Prenatal Diagnosis of Inherited Neurologic Diseases

FORTY-TWO HEREDITARY METABOLIC disorders are potentially diagnosable before birth; the diagnosis has been made prenatally in 14 of them. These disorders are transmitted as either autosomal recessive traits or X-linked recessive traits with a 25 percent recurrence risk in subsequent siblings of an affected child. Nearly all these disorders are fatal, untreatable and involve severe mental retardation. In addition to these metabolic disorders, numerous chromosomal defects, most of which increase in frequency with advancing maternal age (highest risk group, mothers over 40), can be diagnosed prenatally. The optimal time for amniocentesis is at 16 to 18 weeks of pregnancy. In California, second trimester diagnostic amniocentesis has been performed most frequently at medical school affiliated hospitals, including UC Davis, UC San Francisco, Stanford, USC, UCLA, Loma Linda, UC Irvine and UC San Diego.

JOHN S. O'BRIEN, M.D.

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O'Brien JS: How we detect mental retardation before birth. *Med Times* 99:103-108, Feb 1971

Brain Death

CARDIAC TRANSPLANTATION AND ITS dramatic life-saving potential require viable donor organs. Salvage of such organs necessitated modification of the traditional concept of death with the introduction of "brain or cerebral death" as tantamount to death despite the presence of cardiac rhythm. Currently agreed upon criteria hinges upon electrical evidences indicating no spontaneous brain activity. Thus, a comatose patient, in the absence of sedative over-dosage or hypothermia, demonstrating two consecutive one-half

hour "flat or isoelectric electroencephalograms" (EEG) over a 24-hour interval is recognized to have irreversible coma.

FRANK M. YATSU, M.D.

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Treatment of Cerebral Edema

CEREBRAL EDEMA HAS been demonstrated to be the cause of significant morbidity and mortality in association with trauma, neoplasm, infarction, infection, and toxic and metabolic disorders of the nervous system. Dehydration of the acutely swollen brain can be rapidly produced in 20 to 30 minutes by intravenous infusion of a urea solution by creating an osmotic gradient for water to leave brain. A 20 percent mannitol solution in distilled water can be administered in the same manner and with much the same results. Another technique of reducing cerebral swelling is to passively hyperventilate which will reduce PaCO_2 and result in cerebral vasoconstriction. Subacute or chronic cerebral edema can be reduced for weeks or months with dexamethasone 4 mg every 6 hours. Within 24 hours, patients may show an improvement in the state of consciousness and in the levels of their vital signs.

ROGER N. ROSENBERG, M.D.

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Reulen HJ, Samii M, Fenske K, et al: Electrolytes fluid and energy metabolism in traumatic brain edema. *J Neural Neurosurg Psychiatry* 33:714-715, Oct 1970

Normal Pressure Hydrocephalus

"NORMAL PRESSURE OR OCCULT hydrocephalus" represents a landmark recognition of a treatable dementia. This entity is characterized by spasticity with hyper-reflexia, ataxia, occasional urinary incontinence and dementia. Invariably, the spinal fluid pressure is normal, pneumoencephalography demonstrates dilated ventricles with failure of air to pass over the cerebral cortex, radioactive iodinated serum albumin (RISA) in-

jected into the lumbar subarachnoid space refluxes into the ventricular system rather than pass over the cerebral cortex, and the spinal fluid absorption is defective as demonstrated with the "flush" test. In this syndrome, ventriculoatrial shunting has frequently resulted in dramatic improvement in the clinical status of these patients.

FRANK M. YATSU, M.D.

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Treatment of Febrile Seizures

GENERALIZED CONVULSIONS associated with fever constitute a common neurological problem in children under three years of age. Whether and how the patient subject to febrile convulsions should be treated continues to be a subject of controversy. The ideal prophylactic therapy consists of prevention of sudden rises of temperature with aspirin; this is obviously a difficult and impractical approach. The use of aspirin and phenobarbital when the child is afflicted with a febrile illness has been recommended by some observers, while the continuous administration of an anti-convulsant agent—phenobarbital or dilantin—is advocated by others. Recent studies suggest that diphenylhydantoin is ineffective in preventing febrile convulsions even when effective serum concentrations of the drug are achieved. On the other hand, phenobarbital administered twice a day in double the normal dose for three days (60 to 150 mg per day depending on weight) followed by a maintenance dose given twice daily (30 to 75 mg per day) appears to be effective prophylactic treatment provided blood levels of the drug are maintained between 10 and 20 micrograms per ml. Since adequate blood levels usually cannot be achieved in less than three days, intermittent therapy is bound to be ineffective.

PIERRE M. DREYFUS, M.D.

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The Neurology of Drug Abuse

COMPLICATIONS ARISING from drug abuse frequently mimic primary medical and neurological disorders. Familiar examples are subacute bacterial endocarditis and mycotic aneurysm following intravenous heroin, seizures with barbiturates, and organic psychosis after amphetamines. Recently, the occurrences of strokes and subarachnoid hemorrhages (SAH) have dramatically brought to the attention of practitioners yet another disabling and serious complication of drug abuse. The mechanisms of stroke and SAH are not completely understood, but they relate to (1) allergic vasculitis, (2) vascular spasm, or (3) intense hypertension.

FRANK M. YATSU, M.D.

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Prophylaxis of Vascular Headaches

METHYSERGIDE (Sansert®, Sandoz), 2 to 8 mg daily, provides effective headache prevention in 50 to 70 percent of patients with migraine and other vascular headaches. Serious side effects associated with prolonged use of methysergide include peripheral vascular insufficiency and retroperitoneal, cardiac valvular, and pleuropulmonary fibrosis. Patients receiving the drug should be examined monthly for such side effects and, in addition to frequent blood and urine studies, should have chest films, electrocardiograms and intravenous pyelograms performed at least yearly. The risk of side effects is reduced by stopping the drug for one month every six months. The use of methysergide should be restricted primarily to patients with one or more severe migraine headaches monthly and patients with cluster headaches. Some patients will find ergotamine tartrate, 0.5 to 1.0 mg daily, as effective as methysergide but with a much lower incidence of serious side effects.

J. CARROLL RAMSEYER, M.D.

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Medical Treatment of Trigeminal Neuralgia

SEVERE PAROXYSMAL FACIAL pain restricted to the distribution of one or two divisions of one trigeminal nerve can be controlled in most patients by carbamazepine (Tegretol®, Geigy), 200 to 1200 mg daily. Other facial pains, aside from the rare case of glossopharyngeal neuralgia, are not helped by this drug. Because of rare adverse effects, including bone marrow depression and altered liver and renal function, patients receiving carbamazepine must be followed closely and appropriate laboratory studies performed periodically. Since patients with trigeminal neuralgia frequently experience spontaneous remissions, attempts to discontinue the drug should be made every few months. When carbamazepine alone is ineffective, the addition of diphenylhydantoin, 200 to 400 mg daily, may be helpful. Since carbamazepine has been available, very few patients with trigeminal neuralgia require surgical treatment.

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Amols W: A new drug for trigeminal neuralgia. *Trans Am Neurol Assoc* 91:163-164, 1966

Current Areas of Investigation on the Medical Management of Stroke

MEDICAL MANAGEMENT OF STROKES is currently aimed at the unresolved problems of (1) reducing cerebral edema, (2) increasing cerebral blood flow (CBF), and (3) reducing platelet agglutination. Reports on the use of dexamethasone aimed at reducing cerebral edema following a stroke indicate a mild beneficial effect on the neurological status, but further controlled studies are required for proper assessment.

Increasing CBF to ischemic areas adjacent a cerebral infarct with various vasodilators and with blood pressure control remains highly controversial. Although complex and sophisticated brain scanning techniques quantitating regional CBF yield conflicting information, continued investigations should clarify these issues.

Reduction of platelet agglutination by inhibiting its release of adenosine diphosphate (ADP) with acetylated salicylic acid (ASA) or dipyridamole is a potentially effective means of treating transient ischemic attacks (TIA). Preliminary clinical studies supported by basic research on platelet physiology indicate a central role played by platelets in TIA and arterial thrombosis. Current extension of these investigations will shed important light on this critical problem.

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Cervical Spondylosis—The Overlooked Cause of Impaired Gait

CERVICAL SPONDYLOSIS is a degenerative disease of the cervical intervertebral discs which results in injury to surrounding structures and which may *not* always be diagnosed by plain cervical spine films. There is often progressive myelopathy, with no significant cervical or brachial pain, which presents as a progressive gait disturbance. This is generally due to corticospinal tract disease but it is sometimes the result of proprioceptive tract involvement at a time when there is little evidence of motor tract involvement. Although the spinal cord compression is classically demonstrated and localized by myelography, it is possible to screen for a partial or complete block by performing lumbar CFS manometrics with a sensitive strain gauge transducer which may show abnormalities not seen with classical open-tube manometry.

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Muscle Biopsy in the Diagnosis of Neuromuscular Disease

MUSCLE BIOPSIES HAVE become increasingly helpful in the clinical evaluation of the patient with neuromuscular disease. Careful muscle biopsy is especially indicated in the "floppy child" syndrome. One or preferably two separate muscles

50 percent weakened should be chosen. Care should be taken to avoid sampling a muscle previously needled or one into which anesthetic has been injected. Contraction artifact can be avoided by the use of an isometric clamp. Routine fixation and stains suffice in most patients but in complicated cases histochemistry on fresh frozen tissue and electron microscopy may be necessary. Denervating diseases produce fascicles of atrophic fibers while myopathies result in scattered necrotic fibers of varying size with increased connective tissue and fat. Inflammatory changes are characteristic of the polymyositis syndrome. Since biopsies are rarely pathognomonic for specific entities (including muscular dystrophy) the information obtained must be correlated with clinical aspects, electromyography, and serum enzymes.

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 Pearson CM, Coleman RF, Fowler WM, et al: Skeletal muscle—Basic aspects and illustrative new diseases. *Ann Intern Med* 67:614-650, Sep 1967

Usefulness of Brain Scanning

THE BRAIN SCAN has become a clinically valuable diagnostic procedure in the evaluation of a variety of neurologic disorders including brain tumor, abscess, AV malformation, cerebral infarction, subdural hematoma, intracerebral hemorrhage and others. The technique is readily available in most communities and can be performed on an outpatient basis or on severely debilitated patients. The overall diagnostic accuracy of the brain scan compares favorably with other diagnostic procedures such as cerebral arteriography and pneumoencephalography-ventriculography. The primary advantage of brain scanning is that it is a non-invasive technique which can be repeated as required. Although the brain scan is incapable of accurately differentiating between various pathological lesions, the location and approximate size and shape of the lesion may be determined. In addition to obtaining the required four standard views of the head at the appropriate time (usually 1 to 3 hours after injection) many nuclear medicine laboratories record the distribution of the tracer immediately after its injection and during its circulation through the cerebral vessels at 3-second intervals for approximately

20 seconds. This technique can, in some instances, suggest gross alterations in the circulatory dynamics such as in cerebral vascular occlusions and AV malformations.

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Electrodiagnostic Studies in Neuromuscular Disease

NEEDLE ELECTROMYOGRAPHY (EMG) and nerve conduction velocity tests are currently the most useful and popular of the electrodiagnostic studies. Electromyography—by means of a recording needle inserted into the muscle, with an amplifier and oscillographic and loudspeaker displays—provides data concerning the electrical activity of resting and contracting muscle fibers. Interpretation of this data allows differentiation of disorders involving the lower motor neuron from myopathic disorders. Further division of lower motor neuron disorders into those involving the anterior horn cell proper and those affecting the peripheral nerves is often possible, especially when nerve conduction velocities are also determined. Electrodiagnostic studies are particularly helpful in the evaluation of neuromuscular disease in infants and children and in adults with chronic anterior horn cell disease. Electrodiagnostic findings alone are rarely diagnostic of a specific entity and thus should always be correlated with clinical findings and other appropriate laboratory studies.

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Detection of the Muscular Dystrophy Carrier

WHEN FAMILIAL, DUCHENNE muscular dystrophy is inherited in an x-linked recessive manner, with only males being affected. To prevent additional dystrophic male offspring, early detection of carriers is mandatory. The female carrier, even though clinically normal, has a small proportion

of dystrophic muscle fibers, which may be reflected by a modest increase in serum CPK. Other enzymes are less sensitive. Approximately 80 percent of all known carriers have elevated CPK levels, especially if three determinations are averaged and the studies are done early in life. In addition to the patient's mother, female siblings and maternal aunts should also be tested. In a small number of carriers with normal enzymes, electromyography and muscle biopsy are abnormal. Since there is a 50 percent chance that a male born to a known carrier will be dystrophic, prenatal sex determination by amniocentesis may be indicated in certain situations. Enzymes are not elevated in clinically normal carriers of other dystrophies. However, all family members should be examined for evidence of inapparent muscle disease.

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Serum Enzymes in the Diagnosis of Neuromuscular Disorders

THE DETERMINATION OF SERUM enzymes has replaced urinary creatine and creatinine excretion in the evaluation of neuromuscular disease. Serum enzymes are elevated in proportion to the severity and rapidity of myonecrosis. Thus in acute polymyositis, rhabdomyolysis and the early stages of Duchenne muscular dystrophy levels several hundred times normal are seen. Myopathies such as limb-girdle dystrophy, which evolve more slowly, show a modest change or no elevation at all. Denervating diseases are infrequently associated with significant elevation unless rapid and widespread (example, amyotrophic lateral sclerosis). Of the many enzymes which are released from damaged muscle, creatine phosphokinase (CPK) is by far the most specific since it is present in only minute amounts in liver, red cells and most other organs. In polymyositis and dermatomyositis the CPK level is a good indicator

of impending flare or disease activity as well as response to treatment. In Duchenne muscular dystrophy levels drop as the disease worsens and may be normal after puberty. Hypothyroidism may elevate CPK without actual myopathy. Serum aldolase usually follows CPK alterations while SGOT and SGPT levels usually run parallel.

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Facial Nerve Excitability Tests and Prognosis in Bell's Palsy

THE USEFULNESS OF STEROIDS or decompressive surgical procedure in acute Bell's palsy is still controversial because of the high spontaneous recovery rate and the difficulty of predicting the prognosis in the first few days of paralysis. Determination of the threshold of responsiveness of the facial nerve to electrical stimulation allows prediction of a good recovery in 85 percent if the excitability is maintained during the paralytic phase and only 20 percent good recovery if excitability is lost. The test should be repeated every other day and if the response of the nerve is lost, then decompressive operation may be indicated. A new acoustic impedance method allows assessment of a middle ear reflex involving the stapedius muscle and thus a portion of the facial nerve proximal to the chorda tympani may even be monitored. The careful correlation of the above tests with results of taste and tearing testing may allow improved selection of surgical routes for decompression of the facial nerve and offer a greater chance of evaluating results of therapy in an area where well controlled studies are yet to be done.

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Ox, NO_x, PAN and SO_x – When and How Are They Toxic?

“OX” STANDS FOR OXIDANT, the index of severity of photochemical smog. Most of what is measured is ozone. The next most abundant oxidant is nitrogen dioxide (NO₂). Neither of these accounts for the eye and respiratory tract irritation from photochemical smog. The measurement is made by bubbling gas samples through potassium iodide solution and a color change is observed. Formaldehyde, which is not an oxidant, may account for eye irritation, but peroxy-acetyl nitrate (PAN) may account for some of it also.

“NO_x” stands for the oxides of nitrogen. It includes the bland, colorless nitric oxide (NO), the orange-brown irritating but slowly acting, nitrogen dioxide (NO₂) and its equilibrium form (N₂O₄). It does not refer to the N₂O, the anesthetic, fun-loving, substance. Dr. Goldstein’s article elsewhere in this journal describes the toxicological importance of nitrogen dioxide.

PAN is a substance newly discovered in the spectroscopic analysis of photochemical smog. It spontaneously detonates in concentrated form and it is present at less than a tenth of the concentration of ozone. PAN is capable of breaking down in the airway to yield nitrogen oxides and possibly active forms of molecular oxygen. It is a substance which has been little studied toxicologically, partly because it is so difficult to handle.

“SO_x” stands for sulfur oxides. Most of it is sulfur dioxide (SO₂). A portion of it, some say not more than 10 percent, may be oxidized to sulfur trioxide, the anhydride of sulfuric acid. Photochemical oxidation may convert SO₂ to sulfuric acid mist, which is several times more toxic.

Oxidation may be facilitated by submicron particles which absorb SO₂ and which can carry the absorbed SO_x deep into the pulmonary system.

These are the major atmospheric pollutants of concern. Each one of these four symbols stands for an indeterminate chemical mixture.

PAN, for example, is also used to represent the whole family of similar substances including peroxy-benzyl nitrate and peroxy-propionyl nitrate, in which case the designation is usually PANS.

All four of these classes of material are in a dynamic state in the atmosphere. They interact one with the other. The sulfur oxides may be made more toxic by oxidation by ozone occurring in the atmosphere, the ozone will interact with nitric oxide to form molecular oxygen (O₂) and nitrogen dioxide. The conversion of NO to NO₂ is greatly enhanced by the presence of hydrocarbons and this reaction produces PAN as one of its by-products.

What is important to physicians is whether or not, and in what circumstances, these substances are toxic to Californians. Goldstein’s review article on oxides of nitrogen discusses one of the biggest gaps in our knowledge, namely, whether nitrogen oxides cause chronic respiratory disease in man. Given these uncertainties, and the number of persons possibly affected, we have grossly insufficient knowledge, from either experimental or epidemiologic studies, concerning the importance of oxidants and oxides of nitrogen in chronic respiratory disease.

Our knowledge about sulfur dioxide is more adequate. In the presence of particulate matter, sulfur dioxide air pollution over a long period has been accepted by British epidemiologists as a causal factor in chronic bronchitis. Whether it may do this in the absence of cigarette smoking is not so clear. It is conceivable that re-analysis of the epidemiologic data relating pollution to chronic respiratory diseases in Great Britain might indicate that non smokers are rarely affected, in relation to the effects reported in smokers.

If one asks whether or not air pollution at a given time and place is toxic, part of the problem is that "toxicity" is undergoing a redefinition. We consider it relevant to the toxicity of a given type of exposure to ask questions like: "Does it increase the body burden of a potentially harmful material?" or "Does it interfere with an important physiological or biochemical function?" All of the well-studied agents, including ozone, nitrogen dioxide, and sulfuric acid as well as SO_2 , do increase airway resistance at concentrations within a reasonable range of those which occur in community air pollution. The relationship of repeated reversible impairment to long-term effects is not well defined.

In the case of PAN, very little research has been done, but it would be remarkable if something which has the irritating potential of this material, would not ultimately be shown to affect airway resistance at sufficient concentrations.

Concentrations which are occurring in California can affect the health of unusually sensitive groups. Such effects have been shown to occur with ozone exposures, and in all likelihood occur from nitrogen dioxide and sulfur dioxide. The latter two classes of exposures are relatively uncommon.

Dose-response information is summarized in the Air Quality Criteria Reports of the National Air Pollution Control Office of the Environmental Protection Agency. Such reports are available for sulfur oxides, particulate matter, photochemical oxidants including ozone, carbon monoxide, hydrocarbons, and oxides of nitrogen.*

Oxidant concentrations and nitrogen dioxide concentrations sufficient to produce alterations in lung function are uncommon outside the Los Angeles basin. High oxidant readings are occurring with increasing frequency in the Eastern parts of the basin (San Bernardino and Riverside) relative to their previous occurrence in such places as Pasadena and Burbank. This probably reflects the impact of motor vehicle exhaust control in removing the more rapidly reactive hydrocarbons and increasing the emissions of oxides of nitrogen.

Ozone concentrations in excess of 0.5 parts per million activates the air pollution alert system in Los Angeles County.

*These may be obtained from the Government Printing Office Book Store, 450 Golden Gate Avenue, San Francisco, California 94102 at \$1.50 each: AP-49 Particulate Matter, AP-50 Sulfur Oxides, AP-62 Carbon Monoxide, AP-63 Photochemical Oxidants, AP-64 Hydrocarbons, AP-84 Nitrogen Oxides.

These major air pollutants are factors in the aggravation of symptoms of chronic respiratory disease. It is difficult to determine how many susceptible persons are affected. The Health Departments of Southern California counties, the California Medical Association and the California State Department of Public Health are co-operating in an effort to establish an air pollution health warning system, such that when concentrations in excess of 0.2 parts per million of oxidant are predicted to occur, or 1 part per million of oxides of nitrogen, persons in the affected areas who are previously designated by their physicians will be notified that they are at an unusual risk. They can then take the necessary steps to reduce physical activities, stay indoors, and decrease (if they persist in their habit) their exposure to cigarette smoke.

As to whether these materials produce classical toxicity—that is, morphological change—at ambient concentrations, we must answer at the moment that we do not know for sure. For the populations exposed to smog, this may not be a very interesting question.

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The Biologic Premise

THE BIOLOGIC PREMISE to be discussed here assumes that medicine and the society it serves are entering an age when the scientific approach to human problems will displace the doctrinaire, when the biologic character of human society will be generally acknowledged, and when health will be understood as a state of satisfactory adjustment between a "biologic" human being and his "biologic" physical, emotional and social environment. It further assumes that there will be needed a scientist who is also a practitioner who will develop and apply the new disciplines of human biology which will be necessary and forthcoming. It suggests further that the physician of today is the prototype, or perhaps the genotype, of what will be needed and that he can become this scientist practitioner of human biology simply as a

natural extension of his traditional role as the principal scientist and practitioner in health care.

There is much to support this premise. As more and more science is taught in schools and as scientific knowledge becomes more necessary to operate a more technologic society, it seems likely, if not inevitable, that the approach and methodology of science will become the framework or matrix of cultural thought. As this occurs, dogma and the doctrinaire, whether in science, religious belief or social theory, will be questioned and subjected to test by experiment. If found wanting, they will be exposed and expunged. This has already begun to occur. Human society and human institutions are composed of human beings and are themselves extensions of human nature and human behavior. Just as science established the biologic nature of man during the last century so it is likely to establish the biologic nature of human society in this. A biologic society and its human institutions may properly be considered as subject to biologic law and can therefore be examined in terms of biologic principles such as birth, maturation, adjustment, adaptation, homeostasis, fitness, unfitness, survival or death. Health in a biologic society in an age of science therefore not only requires a satisfactory adjustment between a biologic human being and his biologic—that is, physical, emotional and social—environment, but it also requires that there be an understanding in biologic terms of the nature of the human being, the nature of his environment and the nature of the interaction between them. Health in a biologic society in an age of science obviously also requires that there be scholarship in the field of human biology and practitioners of the art and science to help correct what is defective and to strengthen what is weak in the human being and in his physical, emotional and social environment.

The skills of the physician, his knowledge of human biology, his approach to human problems through techniques of diagnosis, treatment, prevention and rehabilitation are what will be needed. What is needed now is acceptance of the proposition that a technologic society will develop a scientific approach and methodology as the ground substance of its social and cultural thought, that human institutions are as fundamentally biologic in nature as are the human beings they comprise, and that health is a biologic state of physical, mental and social well-being

within this conceptual framework. The physician can then easily and naturally evolve into the scientist and practitioner of this new human biology, and organized medicine can be his instrument to hasten the advent of a biologic society in a scientific age and to promote the art and science of medicine within this framework.

—MSMW

Acute Renal Failure: Prevention, Prophylaxis And Progress

IN HIS EXCELLENT and readable discussion of acute renal failure in this issue of *CALIFORNIA MEDICINE*, R. W. Schrier points out that the incidence and mortality of this condition in the U.S. Armed Forces combatants have decreased steadily and significantly from World War I to the present. This improvement has been attributed to vast improvement in evacuation procedures and the increasing availability of adequate dialysis facilities and personnel. A similar trend has been obvious in the civilian population as well. Hamburger¹ reports that the mortality from acute renal failure in women with septic abortion fell from 70 percent to 10 percent with the availability of dialysis. The improved mortality rate, then, is closely related to the development of modern techniques of dialysis. Maxwell's pioneering efforts² have led to the development of simple methods of access to the peritoneal membrane, and the availability of commercially prepared peritoneal dialysis solution has made it possible to dialyze in almost any hospital setting. In addition, the hemodialysis procedure has been simplified and established in many centers across the country within reach of almost any patient in need.

This favorable mortality experience in the military and elsewhere is important, because ever since the introduction of dialysis into the management of acute renal failure by Kolff in 1944³ argument has continued over the proof of its value.⁴⁻⁶ In 1960, Teschan⁷ published the first significant study on the value of "prophylactic

hemodialysis" and firmly established its effectiveness in the treatment of acute renal failure. In recent years the value of dialysis again has been questioned because large dialysis centers with extensive experience have noted steadily increasing mortality despite earlier and more intensive use of dialysis. This rise in mortality is attributed to the constant increment of the age and the complexity and seriousness of illness of the patients admitted for treatment. Acute renal failure following surgical operation for ruptured aorta and open heart operations provides typical examples of these high mortality categories. Thus, it has become apparent that if any doubt still exists over the value of dialysis in the management of acute renal failure, the large centers will have to devise a way to calculate what the expected mortality for a given disease would be in the absence of acute renal failure and subtract that from the gross mortality experience. For example, let us say the mortality rate from acute pancreatitis is 60 percent without acute renal failure and 100 percent with acute renal failure. If the mortality among well-dialyzed patients with acute pancreatitis approaches 60 percent, there can be little doubt of the value of dialysis. In other words, proper use of dialysis should be expected to reduce mortality in a particular disease category only to the level expected in patients with that disease who do not have acute renal failure.

Experience clearly indicates that, to be successful, dialysis must be sufficient to maintain the patient free of all adverse effects of uremia.⁷ In the absence of better criteria, the usual goal is to maintain the blood urea nitrogen below 100 mg per 100 ml at all times, as was done in the case presented to Dr. Schrier. This therapeutic principle means that care must be taken by those physicians in smaller hospitals who would institute peritoneal dialysis on an occasional basis without being able to provide hemodialysis back-up. As Schrier points out, many patients in whom acute renal failure develops are so catabolic that peritoneal dialysis, even when performed daily, is not efficient enough to prevent uremia. Hence, if peritoneal dialysis is instituted, back-up hemodialysis always should be readily available. If it is not, the patient should be moved as soon as possible to a center where it is.

In his discussion of the management of acute renal failure, Schrier ignores the more conservative methods. There is no doubt that protein re-

striction can decrease the blood urea nitrogen and cause symptomatic improvement in uremic patients. However, since the objective of therapy is to dialyze prophylactically to prevent the appearance of uremic symptoms, protein restriction is of little value. The patient whose renal failure has progressed to the point at which protein restriction is necessary to keep him free of symptoms is best treated by dialysis.

The reduction of the incidence of acute renal failure in the Viet Nam as compared with the Korean experience is of great importance for civilian medicine because it illustrates the value of prophylaxis in the prevention of acute renal failure. In particular, the prevention or shortening of a period of vascular collapse seems to be of basic importance, together with the prophylactic use of mannitol. And yet recent experience in our own center underlines the point that even the most careful prophylaxis does not prevent acute renal failure in some patients undergoing open heart operations. Just why it does not remains obscure. This experience in turn confirms Schrier's conclusion that despite a great deal of clinical and basic research on the pathogenesis of acute renal failure the exact mechanism and the real cause of the temporary but reversible acute renal failure remain almost as obscure as during the intensive investigations following World War II. Of interest in this regard is that theories proposed 25 years ago to explain the pathogenesis of acute renal failure, after being thoroughly discredited (or so it seemed) and maligned in the interim, appear again to be valid today. Trueta in 1947⁸ demonstrated the redistribution of blood flow between the cortex and medulla and the chemical and physical factors which influence cortical blood flow, and stated: "Our experimental findings lend support to the theory that renal anoxia, or, as we should term it, cortical anoxia, plays an important part in the development of the renal failure of crush syndrome."

Hollenberg,⁹ using the ¹³³xenon washout technique, recently has demonstrated that acute renal failure of various causes is associated with a decrease in cortical blood flow.

In 1947, Goormaghtigh¹⁰ demonstrated "glandular transformation of the media of the preglomerular arterioles" in the crush syndrome and further observed: "I believe that renal deficiency observed in the crush syndrome is the result of

vasoconstriction involving first the postglomerular arterioles and later the glomerular tufts." He further suggested that the vasoactive substance produced in the preglomerular arteriole may be responsible for this vasoconstriction.

More recently, Brown et al¹¹ found elevated renin levels in patients with acute renal failure, giving more credence to Goormaghtigh's hypothesis.

Finally, we very much like Schrier's definition of terms. We would shorten his definition of acute renal failure to *an acute impairment of renal function which is not reversible by manipulation of extrarenal factors*. Use of this definition then makes other terms more precise and meaningful. Thus, prerenal azotemia describes all conditions amenable to manipulation of the circulation and fluid status, and obstructive renal failure remains the third basic cause of oliguria. We agree with Schrier that the term *acute tubular necrosis* is not a clinical diagnosis but a pathological diagnosis and should be used sparingly, since this lesion appears so rarely among patients with acute renal failure.

Great though the improvement in the mortality from acute renal failure has been, it is probable that further improvement can be brought about by early, vigorous, preventive dialysis. Because of the increasingly severe nature of the diseases associated with acute renal failure, patients will continue to die *with* acute renal failure. However, with the methods and facilities now available, no patient should die *of* acute renal failure.

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Dealing in Futures

Part III—Planning in CMA

TWO PREVIOUS EDITORIALS in these columns have called attention to the problems of medicine and democratic societies when it comes to dealing in futures—that is, investing time, effort, resources and money today, in what can only be expected to pay off at some time in the future. The inherent weaknesses of democratic societies, be they institutions, organizations or governments, when it comes to thinking or planning very effectively much beyond the next election, were noted. In the world as it is today and will be tomorrow, this is a kind of weakness which can prove fatal to the health, well-being and even survival, not only of the institutions themselves but of the people who belong to them.

Organized medicine must be counted among the democratic institutions which have yet to solve this problem of dealing in futures. Recognizing a need many years ago the California Medical Association took an initial step when it created its Bureau of Research and Planning, the first of its kind in the nation. Although planning was part of the original concept, in practice the research function took precedence and the planning function of the Bureau was never carried through. Next the CMA created the first Committee on the Role of Medicine in Society and assigned it the task of exploring the long-range relationships of medicine with a rapidly changing social and practice environment. Subsequently the Council also established the first Committee on Organizational Review and Planning to be found in any medical society, and charged it with responsibility to recommend actions which would better shape the structure of the organization to perform its changing functions. Thus a troika of planning committees came into being. During the past several years the CMA has also sponsored two major Planning and Goals Conferences in the field of continuing edu-

Part III of an Editorial published in three parts. Parts I and II were published in the July and August issues.

cation, and still more recently the Council itself has begun to hold annual "retreats" or planning sessions. But even with all of this effort, which is quite unusual, even precedent-shattering for a democratic organization, planning and action based on planning in CMA are still less than what is needed for these rapidly moving times. The means for truly dealing in futures for this association still elude discovery or identification. It is to be emphasized that this is a failing in the nature of democratic structure rather than of constituency or of leadership in CMA.

These are serious problems which must be dealt with much better than they are today if the democratic way is to be successful in the face of the growing number and complexity of social and health problems which need to be dealt with in the dimension of long-range time. Somehow or other the members of a democratic society and those chosen to govern it must gain a better perception of what may lie ahead, and a greater awareness of the temporal continuum which relates the problems and the decisions made or not made today, to the past, present and future. This implies that democratic institutions as a whole

must gain a greater capacity to receive and react in informed and responsible fashion to indicators and sensings both from their constituencies and from the environment. It also implies that far better means than now exist must be found to anticipate what lies ahead and to accomplish whatever may be necessary to do now for well-being or even survival in the predictable future.

There is much in all this that is analagous to what takes place in the more highly developed biological systems, and there is also much of human nature. It is a characteristic of physicians that they understand both biological systems and human nature more than most. The CMA has made an important beginning, but it is only a beginning. There is still a very long road ahead. Yet this road must be traveled, and the sooner the better, if our democratic systems are to continue to prevail. It would seem that if organized medicine were to recognize this problem for what it is, and if it could develop some kind of model solution within its own democratic framework, this would be a most significant contribution not only to medicine and health, but to society as a whole.

OFFICE ADMINISTRATION OF PENICILLIN

Do you administer intramuscular penicillin in the office?

"I do, in spite of the fact that I live in a state where there are a great number of malpractice suits. I think the important thing here is that you must be careful to ascertain whether there's any history of allergy to penicillin. I wish I could tell you there was some good test for determining sensitivity to penicillin. The three tests that have been recommended—the basophil degradation, the lymphocyte culture, and the skin test—are all difficult. I think most people now feel that the basophilic test is of no help in determining penicillin allergy. The lymphocytic culture test takes about six days, by which time the patient will have either recovered or died from his illness. The skin test does offer some promise, but it also requires technical skills which might not be available. I think a careful history is the important thing. If the patient has no history of previously receiving penicillin or of sensitivity to penicillin, I think that this agent can be administered intramuscularly in the office."

—EUGENE S. HOPP, M.D., San Francisco
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CASE REPORTS

Hemorrhagic Ascites: An Unusual Complication Of Multiple Myeloma

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POSTMORTEM RECOGNITION of extra-medullary tumor involvement in patients with multiple myeloma is not uncommon¹⁻⁵ but the occurrence of hemorrhagic ascites in human myeloma is distinctly unusual. In the case here reported recurrent hemorrhagic ascites developed 22 months after the diagnosis of multiple myeloma was made.

Report of a Case

The patient, a 45-year-old Caucasian woman, was in good health until early 1968, at which time she was found to be pancytopenic. On physical examination in March 1968 no abnormality was noted. Leukocytes numbered 2,200 per cu

mm, with 46 percent granulocytes, 51 percent lymphocytes and 3 percent monocytes. The hematocrit was 24 percent, hemoglobin 8.0 grams per 100 ml, reticulocyte count 1.2 percent and platelet count 98,000 per cu mm. Bone marrow biopsy revealed patchy infiltration with plasma cells, many of which were immature. However, myelopoiesis and erythropoiesis appeared normal. A direct Coombs' test was positive to a titer of 1:4. Serum protein electrophoresis demonstrated a gamma globulin spike of 5.4 gm per 100 ml. Immunoelectrophoretic analysis revealed the presence of an IgG myeloma protein, type K. Electrophoresis of concentrated urine revealed no abnormal protein. Serum calcium, blood urea nitrogen (BUN), serum creatinine, partial thromboplastin time (PTT), prothrombin time (PT), and bleeding time were all within normal limits. A radiographic skeletal survey revealed no abnormalities.

Following transfusion with two units of packed red blood cells, therapy was initiated with cyclophosphamide, 100 mg a day, and prednisone, 40 mg a day. The subsequent course is depicted in Chart 1. After two weeks of prednisone therapy the Coombs' test was negative.

In November 1969, because of a gradual rise in the myeloma protein and increasing neutropenia in the face of a bone marrow examination demonstrating reduction of myeloid elements and patchy infiltration of immature plasma cells, cyclophosphamide was discontinued. Intermittent four-day therapy with melphalan, 0.25 mg per kg of body weight per day, and prednisone, 2.0 mg per kg per day, was begun 23 November 1969. Six weeks after completion of the second course of this therapy, the patient noted progressive abdominal swelling over a one-week period. On examination elsewhere on 23 February 1970 the

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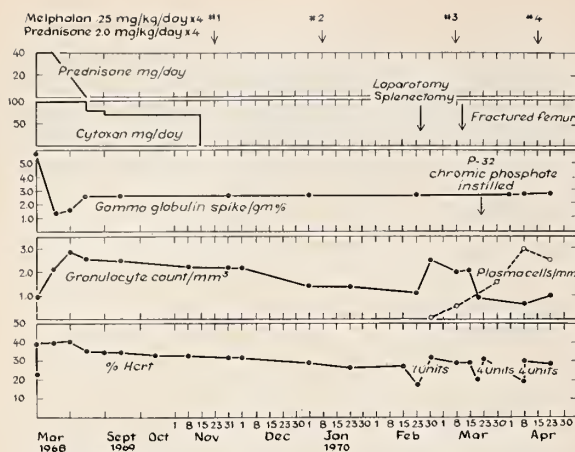


Chart 1.—Course of patient in present case. (Hct =hematocrit).

hematocrit was 18 percent. Transfusion with five units of whole blood raised the hematocrit to 32 percent and the patient was transferred to Stanford University Hospital 36 hours later.

Significant physical findings at that time included mild pallor, tense ascites, and absence of organomegaly or edema. Laboratory studies revealed: Leukocytes 1,300 per cu mm with 78 percent granulocytes and no plasma cells, hematocrit 27 percent, reticulocyte count 2.1 percent and platelet count 57,000 per cu mm. Serum creatinine, serum calcium, BUN and liver function tests were within normal limits. Evidence for a coagulation or hemostatic defect was sought but could not be demonstrated, as evidenced by the following normal studies: PTT, PT, bleeding time (Borchgrevink); thrombin time; clot retraction and plasma euglobulin clot lysis time. Serum protein electrophoresis revealed an albumin of 3.0 gm per 100 ml and a gamma globulin spike of 2.7 gm per 100 ml. There was no proteinuria. Paracentesis yielded non-coagulable sanguinous fluid, studies of which included: hematocrit, 19 percent; leukocytes, 9,000 per cu mm with 95 percent bizarre plasma cells (Figure 1); albumin 2.6 gm and globulin 3.8 gm per 100 ml. Electrophoretic studies of the ascitic fluid were not obtained.

Following transfusion with two units of packed red blood cells, exploratory laparotomy was carried out. Multiple peritoneal nodules and a hemorrhagic 4x4 cm mass adjacent to the right ovary were observed. Splenectomy and a right salpingo-oophorectomy were performed, after which

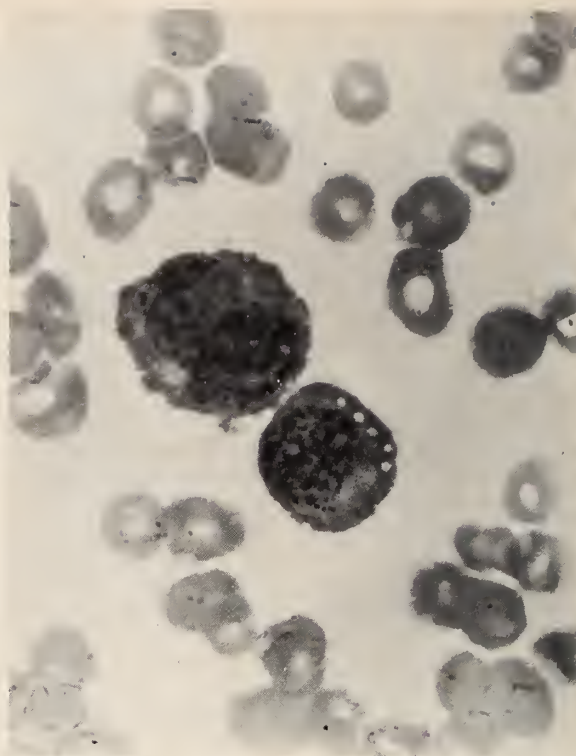


Figure 1.—Representative bizarre plasma cells present in ascitic fluid. (Wright's stain, x 1200).

40 mg of thio-TEPA were instilled into the peritoneal cavity.

The spleen weighed 380 gm and on microscopic examination infiltration of plasma cells was noted. A representative peritoneal nodule (Figure 2) and the right para-ovarian mass proved to be plasmacytomas on microscopic examination. Many of the plasma cells were large and immature.

Following the surgical procedure the patient's course was one of transient improvement, permitting a third course of melphalan-prednisone therapy which was completed 11 March 1970. However, the next day a spontaneous fracture of the right femoral neck occurred which required surgical repair. The ascites gradually reaccumulated and on 21 March 1970 following paracentesis of 3 liters of ascitic fluid, 15 millicuries of radioactive chromic phosphate ($\text{CrP}^{32}\text{O}_4$) were instilled intraperitoneally. There was no recurrence of ascites, but bilateral lower quadrant masses appeared and progressed to a size of approximately 8x8 cm over a three-week period. Despite a fourth course of melphalan-prednisone, the patient steadily deteriorated, and increasing

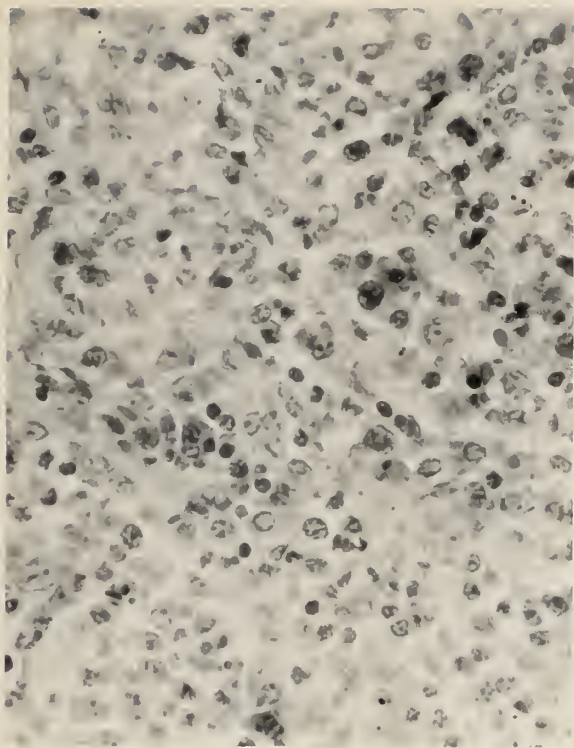


Figure 2.—Section of a representative peritoneal plasmacytoma demonstrating many large, immature plasma cells. (Hematoxylin-eosin, x 320.)

numbers of primitive plasma cells were noted in the peripheral blood. She died 23 April 1970, eight weeks after the onset of ascites, probably from an episode of sepsis. Postmortem examination was not performed.

Comment

Serosal involvement in multiple myeloma is unusual. Pleural¹⁻⁴ as well as pericardial^{1,3,5} involvement has been sporadically noted in necropsy series of patients with multiple myeloma. Additional case reports have described patients with multiple myeloma and pleural effusions containing large numbers of plasma cells,⁶⁻⁸ or pleural effusion clearing with cyclophosphamide therapy.⁹

Peritoneal involvement in myeloma is equally rare. Churg and Gordon¹ noted only one such case at autopsy of 30 myeloma patients. Hayes, Bennett and Heck² found no peritoneal myeloma involvement in 38 patients and noted only three such instances in a review of the literature. Innes and Newall,³ and Carson, Ackerman and Maltby,⁵ noted no peritoneal involvement in 45 and

27 cases respectively of multiple myeloma at postmortem examination. The rarity of peritoneal involvement contrasts with the more common occurrence of extramedullary myeloma in lymph nodes, liver and spleen.³

The appearance of hemorrhagic ascites in the present case is reminiscent of the experimental situation in the BALB/c strain of mice. Multiple peritoneal plasmacytomas and hemorrhagic ascites develop in a high proportion of these mice within 14 months following intraperitoneal injection of mineral oil,¹⁰ or even installation of empty millipore diffusion chambers.¹¹ Plasmacytoma formation outside the peritoneal cavity is not found. However, hemorrhagic ascites in human myeloma is most unusual. Durant and Barry⁹ described a patient with anaplastic multiple myeloma and exudative ascites containing abnormal mononuclear cells, many of which were plasmacytes. The ascites was unresponsive to intracavitary thio-TEPA, but oral cyclophosphamide induced a partial remission. Pruzanski, Platts and Ogryzlo¹² described a patient with plasma cell leukemia in whom ascites developed late in the course of the disease. However, the characteristics of the ascitic fluid were not described in their report and peritoneal implants were not noted at autopsy. An additional patient has been described with plasma cell leukemia and hemorrhagic ascites secondary to spontaneous rupture of an infiltrated spleen.¹³

The appearance of ascites in the present case heralded a rapid deterioration in the clinical course. Intensive therapy with intermittent melphalan-prednisone, as described by Alexanian and coworkers,¹⁴ and intraperitoneal injection of thio-TEPA, did not retard reaccumulation of ascitic fluid. Following the intraperitoneal installation of radioactive chromic phosphate, which has produced a beneficial response in some patients with exudative ascites secondary to lymphoma,¹⁵ ascitic fluid did not reaccumulate. However, the abdominal disease progressed rapidly as manifest by the appearance of bilateral lower quadrant masses.

This case is a further illustration of the protean manifestations of extramedullary myeloma. The diffuse peritoneal disease in this patient supports the contention that anaplastic myeloma may mimic the clinical manifestations of other aggressive disorders of the reticuloendothelial system.³

Summary

Hemorrhagic ascites developed 22 months after the diagnosis of multiple myeloma in a woman 45 years of age. The myeloma protein was of the IgG , kappa chain, type. Examination of the ascitic fluid revealed numerous immature plasma cells. Exploratory laparotomy demonstrated multiple peritoneal plasmacytomas. Therapy with melphalan and prednisone, and intraperitoneal instillation of thio-TEPA, did not retard reaccumulation of ascitic fluid. Following injection of radioactive chromic phosphate the ascites did not recur, but bilateral lower quadrant masses developed and the patient died eight weeks after the onset of ascites.

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Aseptic Meningitis Following Intrathecal Radioiodinated Serum Albumin

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THE INTRATHECAL administration of RISA® (radioactive iodinated serum albumin) has been used extensively since 1964 as one means of visualizing the circulation and dynamics of the cerebrospinal fluid (CSF) in normal and pathological conditions. Untoward reactions have been few.¹⁻⁵ We are reporting two cases of aseptic meningitis following intrathecal injection of RISA.

Case 1. A 78-year-old right-handed woman had a two-year history of progressive dementia, intermittent fluctuation of consciousness, unsteady gait and urinary incontinence. Neurological examination revealed global dementia, snout, suck and bilateral grasp reflexes, brisk symmetrical muscle stretch reflexes and flexor plantar responses. She had a decidedly unsteady gait. An electroencephalogram revealed diffuse slowing. Because of the possibility of "normal pressure hydrocephalus" and its occasional amelioration by removal of a large volume of CSF,^{6,7} a lumbar puncture was performed and 40 ml of CSF was withdrawn. The opening pressure was 75 mm of water; the fluid was normal (Table 1). Within a day the patient appeared brighter and incontinence and ataxia disappeared.

Six days later when spinal puncture was done again, 35 ml of CSF was withdrawn and 1.4 ml of 106 μC per ml RISA (10 mg albumin per ml) was injected. Within four hours shaking chills developed and the temperature was 39.8°C. The patient was confused and lethargic and there was pronounced nuchal rigidity. On lumbar puncture 24 hours after the RISA injection, opening pressure was 100 mm. The fluid was cloudy and slightly xanthochromic with pronounced leukocytosis and elevated protein (Table 1). A Gram stain and a culture of the CSF were negative for pathogens. Since the nature of the meningeal reaction was not known, ampicillin and streptomycin were ad-

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TABLE 1.—Data on Spinal Fluid Before and After Intraspinal Injection of RISA®

	Lumbar Puncture		
	Preliminary	Post RISA 24-hour	Follow-up (5 days)
<i>Case 1:</i>			
Opening pressure	75 mm H ₂ O	100 mm H ₂ O	70 mm H ₂ O
Appearance	clear, colorless	cloudy, xanthoc.	clear, colorless
Cell count			
Leucocytes	0	3,844 (98 percent poly)	5
Erythrocytes	0	3,250	19
Protein	10 mg per 100 ml	282 mg per 100 ml	60 mg per 100 ml
Glucose	80 mg per 100 ml	60 mg per 100 ml	50 mg per 100 ml
Gram stain	Negative	Negative	Negative
Culture	Negative—72-hr.	Negative—72-hr.	Negative—72-hr.
<i>Case 2:</i>		24-hour Post RISA	
Opening pressure (sitting)	340 mm H ₂ O	510 mm H ₂ O	
Appearance	clear, colorless	cloudy, xanthoc.	
Cell count			
Leucocytes	0	4,790 (100 percent poly)	
Erythrocytes	150	431	
Protein	30 mg per 100 ml	545 mg per 100 ml	
Glucose	90 mg per 100 ml	106 mg per 100 ml	
Gram stain	Negative	Negative	
Culture	Negative—72-hr.	Negative—72-hr.	
Blood (leukocytes per cu mm)	8,400	18,000 (86 percent poly)	7,700 (60 percent poly)

ministered. The clinical course was one of rapid improvement; within 48 hours fever and meningeal signs were gone. A lumbar puncture five days after the RISA injection revealed pronounced improvement. There were no observable sequelae to the incident.

Case 2. A 77-year-old right-handed man presented with a history of progressive dementia for at least a year, and recent onset of unsteady gait and urinary incontinence. The past history was notable for alcoholism. Noted on neurological examination were global dementia, snout and suck reflexes, proprioceptive loss in the legs with brisk muscle stretch reflexes and bilateral extensor plantar responses. The gait was unsteady and Romberg's sign was present. Abnormal results of laboratory investigations were: hemoglobin of 8.6 mg per 100 ml, zero uptake of isotope in a Schilling test, and bone marrow consistent with megaloblastic anemia. There was diffuse slowing on an electroencephalogram. To rule out normal pressure hydrocephalus,^{8,9} a lumbar puncture was done and 40 ml of CSF was removed. Then 0.3 ml of RISA (250 μ c per ml, 10 mg of albumin per ml) was injected. The opening pressure on lumbar puncture was 340 mm of water (sitting). The fluid was normal on examination (Table 1).

Within six hours the temperature was 39.6°C,

the patient was somnolent and there was decided nuchal rigidity. On spinal puncture done at the time, the opening pressure was 510 mm (sitting). The fluid was cloudy and xanthochromic, with leukocytosis elevated protein (Table 1). A Gram stain of the CSF was negative, as were cultures at 72 hours. Leukocytes in a specimen of blood drawn at the time of the lumbar puncture numbered 18,000 cells per cu mm with 86 percent polymorphonuclear forms. The patient was given ampicillin prophylactically. Within 24 hours the temperature was 37.6°C and by 72 hours all meningeal signs were absent. Five days later leukocytes numbered 7700 per cu mm of blood, with 60 percent polymorphonuclear cells. The patient subsequently improved on vitamin B₁₂ therapy.

Discussion

Review of our technique confirmed that new, sterile, disposable plastic syringes and tubing had been used. Specimens of each RISA solution that was used were saved and cultured, with negative results. Biological assay for pyrogens also was negative. The skin was cleansed before the lumbar punctures with standard merthiolate solution, which was also sterile on culture.

In a typical study 100 μ c of high specific activity I¹³¹ RISA (250 to 500 μ c per ml) is injected into the

lumbar sac and the distribution of the drug is followed by serial external scintillation scanning of the head at four, 24 and 48 hours.^{1,8,9} Di Chiro¹⁰ recommends the use of a minimal volume (0.2 to 0.4 ml) of RISA (10 mg of albumin per ml). Positioning the patient has no effect on the speed of flow or distribution of the material in the subarachnoid space; however, diluting the RISA with Elliott's B solution or normal saline solution approximately to 10 to 25 percent of the estimated CSF volume (10 to 20 ml of fluid) increases the cephalad passage and provides a more widespread distribution.¹¹ One-third to one-fifth of the injected material reaches the endocranium, giving a total body exposure of 100 millirads and a radiation dose of 1 rad to the central nervous system¹—all within the recognized safety margins. By three hours the tracer substance is visible in the basal cisterns and sylvian fissure; at 24 to 48 hours the radioactivity is over the hemisphere predominantly in the parasagittal area along the superior longitudinal sinus, and by 48 hours the tracer medium has cleared the subarachnoid space, a significant amount being absorbed into the pacchionian granulations.^{1,8,9,12,13,14,15}

Complications of intrathecal RISA recorded in the literature have been few. Bell⁴ and Pinto⁵ reported hyperpyrexia and vomiting as adverse reactions; Detmer and Blacker² in 1965 and Nicol³ in 1967 each recorded a case of aseptic meningitis; both expressed belief the meningeal reaction had a direct correlation with the relatively large amount of albumin in the RISA used. Detmer and Blacker reported CSF pleocytosis (150,000 lymphocytes per cu mm) and a CSF Pandy reaction of 4+ following use of RISA containing 27 mg of albumin. In Nicol's case there was CSF pleocytosis of 980 polymorphonuclear cells and a CSF protein rise from 48 to 106 mg per 100 ml after intrathecal injection of RISA with 100 to 130 mg of albumin.

In Case 1 herein reported, aseptic meningitis developed after an injection of RISA containing a total of 14 mg albumin, with CSF pleocytosis of 3,844 cells (98 percent polymorphonuclear) and a CSF protein rise from 10 to 282 mg per 100 ml. In the second case, using RISA with just 3 mg of albumin resulted in a greater rise in CSF protein, from 30 to 545 mg per 100 ml, and pleocytosis of 4,790 cells (100 percent polymorphonuclear). Thus it appears that the extent of the meningeal response may not reflect the amount of protein injected intrathecally,

Conceivably our second patient's meningitis after only 3 mg of albumin could reflect an idiosyncratic reaction. Although there is evidence in the literature that withdrawal of CSF may be of some significance in causing increased ependymal uptake of radioactive material,^{8,16,17,18} whether our removal of a large volume of CSF before the RISA injection led to or potentiated the meningeal reaction can only be conjectured.

Di Chiro¹⁰ recommended that a minimal volume of 0.2 to 0.4 ml of RISA with high specific activity (250 to 500 μ C per ml) RISA and a low protein concentration (2 to 4 mg of albumin) be used for intrathecal injections. Theoretically, the smaller the amount of antigenically active material introduced in the subarachnoid space, the safer the procedure.^{19,20} However, there has been no serial CSF study following RISA administration, and meningeal reactions may occur far more frequently than suspected.^{21,22}

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Blunt Laryngotracheal Trauma

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BLUNT TRAUMA to the anterior neck resulting in laryngotracheal injury has become an imposing medical problem because of two factors: (1) the increasing number of automobile accidents and (2) certain automobile safety devices which, while often preventing death, cause other kinds of injuries. Several recent reports have dealt with the so-called "padded dash syndrome"^{1,2} in which hyperextension of the neck exposes the larynx and trachea to blunt injury from the dashboard or steering wheel.

Recent cases of blunt laryngotracheal trauma seen at Harbor General Hospital have been reviewed and three were selected for presentation in this report because of the principles of treatment they illustrate.

Reports of Cases

Case 1. A 45-year-old man was seen at Harbor General Hospital after a single vehicle automobile accident. He was agitated and anxious, with inspiratory stridor, hemoptysis, and a hoarse voice. Noted on physical examination were a flattened laryngeal prominence, with subcutaneous cervical emphysema, a flail chest and decreased breath sounds on the right. Tracheotomy was performed to relieve the respiratory distress. Intermediate positive pressure assistance to breathing was begun and right-sided pneumothorax was treated with a chest tube. An x-ray film of the chest showed pneumothorax in about half the right side of the chest, multiple anterior rib fractures and cervical and mediastinal emphysema. Skull and cervical spine x-ray films were negative. Laryngeal repair was deferred because of the chest injuries.

The patient's condition had stabilized by the

fifth day after injury, and open exploration of the neck was performed. Preoperative direct laryngoscopy showed motionless paramedian cords. At operation, a midline vertical fracture of the larynx was seen with underlying edema and contusion of the true and false cords (Figure 1). The cords were not avulsed nor were the arytenoids dislocated. The thyroid cartilage was repaired with stainless steel over a 34 (French) plastic Argyle sump tube which had been previously heated and fashioned with an anterior wedge to provide a keel to maintain the commissure. The top of this keel was warmed and sealed. Edema and hematoma of the anterior neck prevented visualization of the recurrent nerves.

The stent was removed six weeks after operation. A laryngogram was made, and the trachea was decannulated. The airway was fully reconstituted but the voice was hoarse. The left cord had returned to almost normal mobility 40 weeks after operation.

Case 2. A 19-year-old girl who had been beaten with a board had anterior neck and facial injuries. She was in respiratory distress with inspiratory stridor and mild cyanosis on arrival in the emergency room. Immediate tracheotomy was performed to relieve the respiratory obstruction. Physical examination showed mild flattening of the anterior neck with multiple bruises but no lacerations. The right malar complex was flattened, and the mandible had false motion with crepitus in two places. Several teeth were missing. Preoperative x-ray films showed a fracture of the right malar complex with cloudiness of the right antrum, a fracture of the left body and symphysis of the mandible, and cervical emphysema. The cervical spine, chest, and skull were intact.

On laryngoscopic examination the left paramedian cord was seen to be immobile and there was a moderate-sized hematoma on the left false cord and aryepiglottic fold. The left true cord appeared to be avulsed; there was some motion of the right cord. No further injury was observed on esophagoscopy. Open exploration confirmed the avulsion of the left true and left false cords, with midline vertical fracture of the larynx and a trapdoor fracture extending from this fracture to the right (Figure 2). The cricoid cartilage was intact. The left false and true cords were sutured anteriorly onto the thyroid ala, and mu-

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Reprint requests to: Department of Surgery/Head and Neck, University of California, Los Angeles, School of Medicine, Center for the Health Sciences, Los Angeles, Ca. 90024 (Dr. B. W. Jafek).

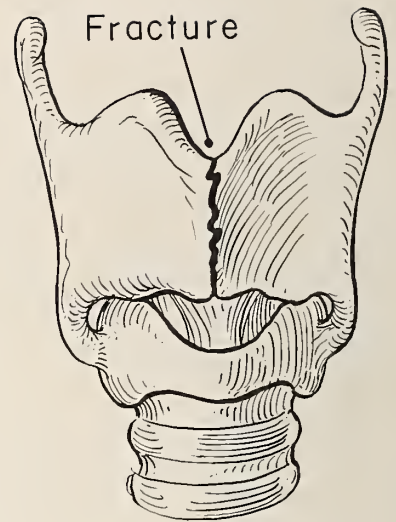
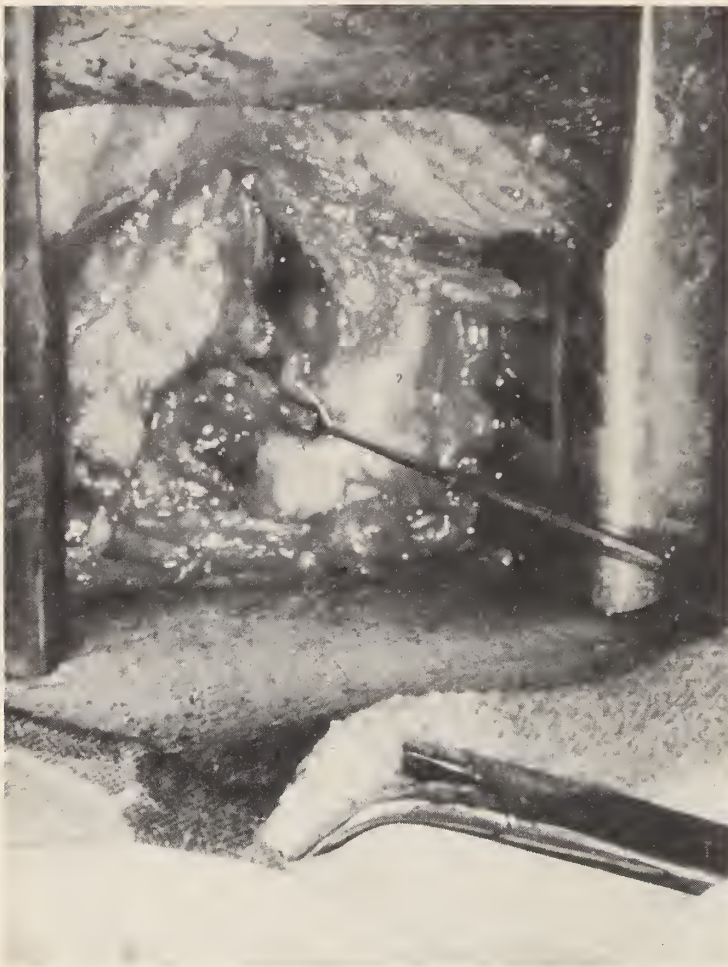


Figure 1.—Photograph of surgical field with diagrammatic representation of laryngeal fracture.

cosa was closed over all bare areas of cartilage within the larynx. The larynx itself was repaired over a 32 (French) stent similar to the one described in Case 1. The stent was positioned with a through-and-through stainless steel wire. The recurrent nerves were not seen. Arch bars were applied following open reduction of the fractures of the mandible and malar complex, and intra-maxillary fixation was carried out.

The patient's postoperative course was complicated by cerebrospinal fluid rhinorrhea, which responded to conservative treatment.

The stent was removed eight weeks after operation and the trachea decannulated. The patient remains hoarse but an adequate airway has been maintained. There is good motion of the right cord, but the left cord remains fixed 40 weeks postoperatively.

Case 3. A 22-year-old man was admitted to

the hospital with hemoptysis, respiratory distress with inspiratory stridor, and hoarseness. He had driven his open sportscar under a chain stretched across a private driveway and had been jerked out by the neck. Physical examination revealed flattening of the anterior neck with superficial laceration across the mandible. Subcutaneous emphysema was severe, and immediate tracheotomy was imperative. This was accomplished with difficulty, as the trachea had retracted into the superior mediastinum and was separated from the cricoid cartilage by approximately 4 cm. It was held in place by paratracheal connective tissue. Chest, skull, and cervical spine x-ray films showed cervical and mediastinal subcutaneous emphysema.

Direct laryngoscopy and esophagoscopy showed the cords to be fixed bilaterally in a paramedian position. Complete laryngotracheal

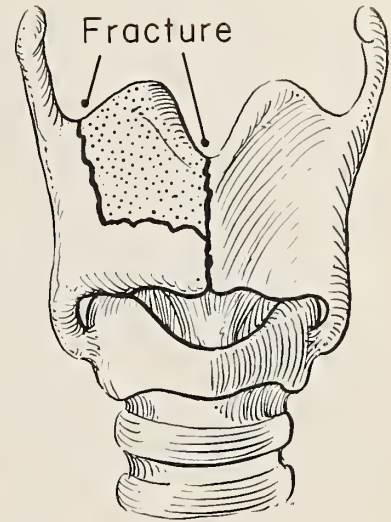
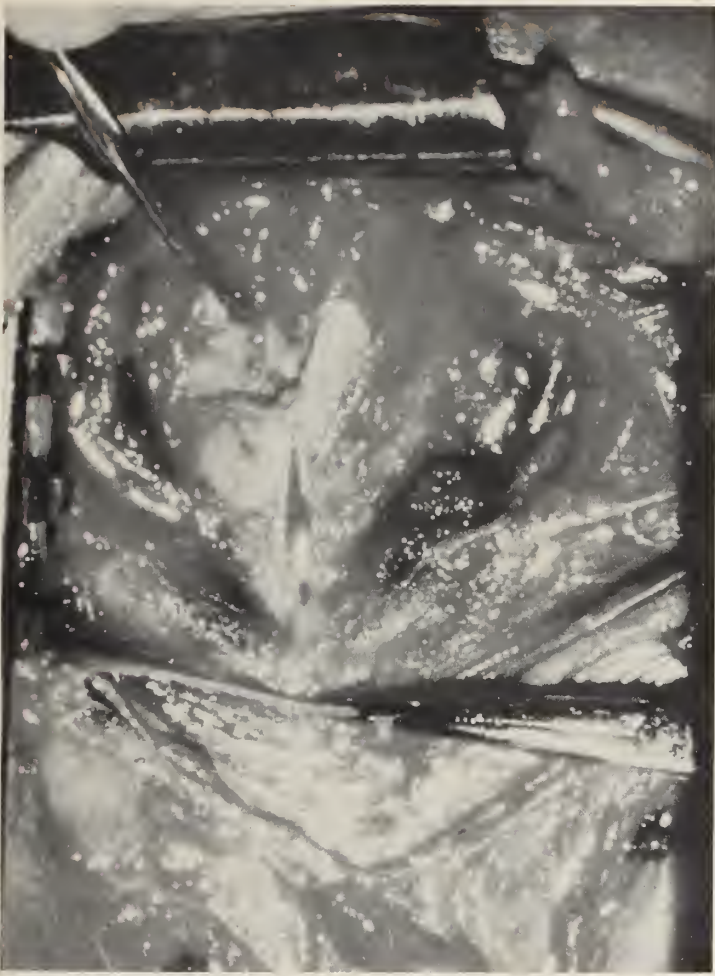


Figure 2.—Photograph of surgical field with diagrammatic representation of midline laryngeal fracture and trapdoor fracture extending to the right.

separation was confirmed. An anterior rent in the esophagus was present with the tracheostomy tube clearly visible through the esophagoscope.

Exploration revealed complete separation of the first tracheal ring from the cricoid cartilage which had two divergent vertical fractures on the left. A transverse crush laceration of the left side of the esophagus extended for approximately half its circumference (Figure 3).

Tracheotomy was done approximately three rings below the avulsion. A nasogastric tube was passed and the esophagus was closed horizontally in two layers. The tracheal and cricoid mucosa was closed with interrupted chromic sutures and the perichondrium overlying the cricoid fracture was reapproximated with No. 35 wire. The first tracheal ring was sutured to the

cricoid laterally and anteriorly over a stent made by filling the finger of a glove with sterile foam rubber. This stent was fixed in place with through-and-through sutures of No. 22 wire.

The stent was removed in six weeks, and after decannulation laminograms of the larynx showed a widely patent airway. Esophagrams showed no evidence of stricture. Indirect laryngoscopy two years later showed paresis of the left cord with normal motion of the right. The patient has slight hoarseness with an adequate glottic chink and normal deglutition.

Discussion

The three cases presented illustrate different types of blunt laryngotracheal injury and the varying requirements of management. The first was a larynx fracture without disruption of the

underlying vocal mechanism. Open repair was delayed temporarily by coexisting injuries which greatly increased the technical problems. In the second case also there was fracture of the larynx but in addition repair of the vocal mechanism was necessary. In the third case, complete avulsion of the trachea from the larynx occurred with laceration through one-half of the circumference of the esophagus, an injury which is usually fatal.³

Each of these patients presented in fairly classic fashion. Each had had trauma to the anterior neck with resultant progressive respiratory distress, cyanosis, hemoptysis, cervical subcutaneous emphysema, and palpable evidence of fracture or laryngotracheal disruption.^{2,4,5} Several investigators have observed that the absence of laceration or the presence of voice (true in each of these cases) does not rule out severe injury to the trachea or larynx.^{1,6} The importance of careful evaluation of coexisting injuries is well illustrated, as these patients had, variously, in addition to their laryngotracheal injuries, complications of cerebrospinal fluid rhinorrhea, esophageal laceration, flail chest, pneumothorax, and severe facial bone and mandible fractures.

Injury occurs because the larynx or trachea is crushed between two immobile objects, the cervical vertebrae and the insulting object, usually a steering wheel or dashboard.⁵ In an automobile accident, the site of injury may be related to the patient's habitus; women with long supple necks are likely to have supraglottic injury.² Tracheal injury may occur because of greatly increased intratracheal pressure, presumably because of glottic closure in anticipation of a collision, followed by blunt trauma to the chest.^{3,7,8} The cricoid cartilage and the first tracheal ring are most often injured because of the position of the larynx in the neck.^{6,9} Because of the elasticity of the intercartilaginous ligaments, avulsion of the trachea allows it to retract into the lower neck or mediastinum, as occurred in Case 3.

Early diagnosis is imperative. Not only the ultimate functional result but also survival itself depend on the therapy.^{1,2} Prompt tracheotomy frequently is life-saving. It may allow the release of previously accumulated air as well as prevent new accumulation which if it finds its way into the mediastinum or pericardium can cause tamponade and death.⁵

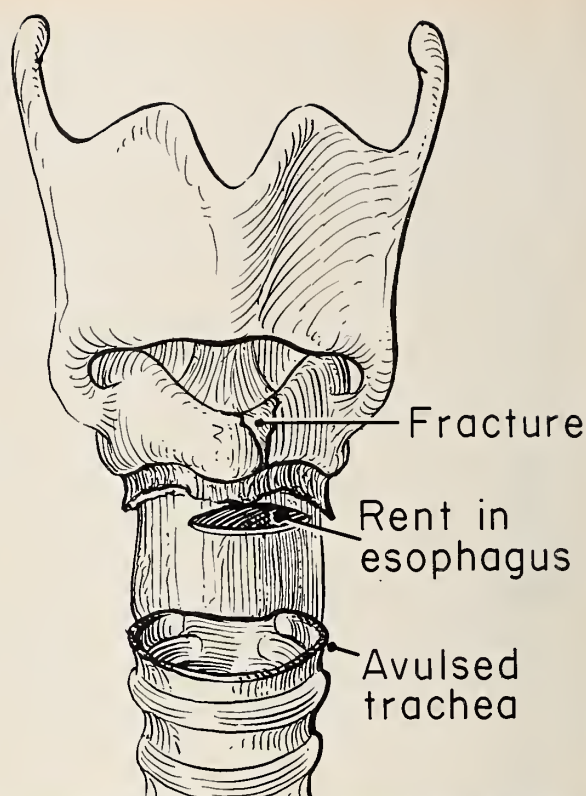


Figure 3.—Diagrammatic representation of cricoid fracture, esophageal laceration, and tracheal avulsion.

Preoperative x-ray examinations are indicated, particularly of the cervical spine.

The incidence of stenosis described in earlier reports^{6,10} can be greatly reduced by early diagnosis and definitive treatment. Endoscopy should be followed by open exploration of the neck where indicated. Accurate apposition of the cut ends of the laryngeal or tracheal mucosa will decrease the incidence of granuloma formation and subsequent stenosis.¹¹ Primary anastomosis over a stent is the treatment accepted by most surgeons. Most use a closed stent,^{1,2,9} but a few prefer an open one to maintain the benefit of normally humidified air.⁴ The stent is left in place two to eight weeks. In our experience, a six-to-eight week period of closed stent has provided good results. Cricoid injuries may require three or four months of stenting.⁵

Esophageal closure in the cases presented was accomplished by the standard two-layer method. A horizontal or, if tension does not permit, a modified T or Y-closure is recommended to avoid subsequent stenosis, a frequent complication of vertical closure.

Anastomosis or primary reconstruction of the recurrent laryngeal nerve is rarely possible, and secondary procedures such as arytenoidectomy or arytenoidopexy may be necessary to restore an adequate airway.

Broad spectrum antibiotics and drainage of the incision are important adjunctive measures.^{2,12,13} The use of steroids remains controversial but may be indicated in the secondary reconstruction of stenotic areas.¹⁴ Few observers recommend them in acute injuries.

Often there is vocal impairment²—hoarseness or whisper—and the patient should be advised of this possibility.

Summary

Three illustrative cases of blunt trauma to the anterior neck resulting in laryngotracheal injuries are presented. The principles of diagnosis and early management are reviewed. Early primary

repair over a stent is advocated in order to restore deglutition, voice, and an anatomical airway.

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LETTERS *to the Editor*

DOA for the AMA and CMA

To the Editor: The editorial in the June, 1971, CALIFORNIA MEDICINE titled "Hara-kiri and Its Consequences" reminds me of a personal experience when I was an assistant police surgeon at Georgia Street Hospital, Los Angeles.

A middle-aged oriental walked off the elevator holding his hands around a bloody shirt and when taken to the examining room it was found he had disemboweled himself without lacerating the intestine. In those days no antibiotics were available. Consequently, aqueous mercurochrome was poured liberally over the exposed intestine and it was replaced in the abdominal cavity and the transverse abdominal wound was closed. No complications ensued and the incision healed by primary intention.

Subsequently it was ascertained that the patient had a severe mental aberration and he was sent to the psychiatric ward of the Los Angeles County General Hospital.

Approximately three months later while I was on duty at the Georgia Street Hospital, a DOA body was brought to the hospital. It was that of the same man I had treated previously.

It was ascertained that upon his release from the psychiatric ward he had boarded a street car to downtown Los Angeles and there took an ele-

vator in a tall building, went to a window and jumped off a fire escape, falling through the roof of an automobile parked below.

It seems to me this case illustrates the points in your editorial. Similarly mental aberrations brought about the petitions for local referenda.

If the statewide opinion poll of CMA succeeds in disavowing the CMA and the AMA, the anticipated cure by the proponents will in the end result in the development of the kinds of consequences anticipated by your editorial, *viz.*, DOA for the AMA and CMA.

JOHN E. KIRKPATRICK, M.D.
San Francisco

A Hot Word from #AB 3,522,477

The following is a letter written by a California physician to the Bureau of Narcotics and Dangerous Drugs after examining the Bureau's new form for persons handling drugs.

United States Department of Justice
Bureau of Narcotics and Dangerous Drugs
P.O. Box 28083, Central Station
Washington, D.C. 20005

Dear Sirs:

The recent form sent to all persons having a legitimate reason for handling drugs represents an appalling, illogical, uninformed, unadvised dictation by a governmental bureaucracy. The instructions and forms demonstrate the usual overly complex and nondirect method of writing.

My main objection is to the new BNDD # with two letters and seven digits allowing for 9,999,999 individual persons and a total of 6,759,999,999 individuals if the letters are utilized. All of these numbers and letters are for a system of less than 300,000 MD's, fewer dentists, even fewer pharmacies and a markedly smaller number of distributors, packagers, wholesalers and manufacturers, and hospitals. HOW DARE THE GOVERNMENT SAY I AM # AB 3,522,477 AMONG A GROUP TOTALING HALF A MILLION OR LESS.

With the judicious use of letters—MDA, MDB, MDC, etc. for physicians; DDA, DDB, DDC, etc. for dentists; PHA, PHB, etc. for pharmacies; M for manufacturers; W for wholesalers; H for hospitals; etc. for packagers, distributors, importers—at the most a four or five digit system would suffice now and have an adequate range for more than the next 50 years.

The practicing and working doctor, dentist and pharmacist already has an excess of paper work and regulation hindering their proper job of giving succor and technical knowledge to ill patients. Some of this odious work can be handled by an ever increasing number of secretaries and typists ADDING TO OVERHEAD AT NO BENEFIT TO THE PATIENT, but the writing of Rx and calling of Rx to pharmacies OUTSIDE of office hours will forever be the individual responsibility of the working physician.

Imagine the percent of error in my small region of practice using one hospital area involving about 250 MD's learning a two letter seven digit number calling in a prescription to any one of 80 nearby pharmacies in our community requiring the proper telling and then hearing of a long, nonsensical, extraneous and maddening number to get some aspirin and codeine or some cough syrup with codeine for a miserable patient who may have seen the doctor already and should stay home resting.

Since the responsibility of action will always remain individual for the MD and DDS and if there is some sadistic fulfillment by whoever insists on a big number system, what is wrong in using the social security number for those individuals and letters and four or five digits for the non-individuals handling drugs?

I was never able to remember my service number except for the last four digits required to get my laundry and at my age the BNDD has not

given adequate reasons to promulgate such an unnecessary system.

This new BNDD system of numbering interferes with the proper flow and providing of health care. Will you all please loudly and constructively complain.

WILLIAM BAXTER, M.D.
Los Altos

EDITOR'S NOTE: The Editor agrees and loudly and constructively complains. If you can't lick 'em join 'em—use a rubber stamp.

Air Pollution, Health Effects and Urban Growth

To the Editor: In his article on air pollution (Calif Med 115:106-107, Jul 1971), Dr. Louis F. Saylor of the California Department of Public Health warns that the smog is increasing faster than anybody can keep up with.

If the population continues to grow at the present rate, he says, air pollution will hurt us plenty. In fact, it already *has* hurt us plenty. School children in Los Angeles are told not to take a deep breath during the alerts. That means they are being deprived of a basic right. "We do not know how to control pollutant emissions enough to reach these [established air-quality] standards," Dr. Saylor says.

He then vaguely talks about the need for better controls and for policies "which would prevent pollution," just as if we had not been talking about that for lo! these twenty years. But he seems to be afraid to come up with the obvious solution: gas rationing.

If you were to analyze the driving habits of the average Californian, you would find that a great deal of this driving is purely for convenience and pleasure. How long are we to tolerate unrestricted transportation, including transportation for the most ridiculous purposes, for everybody who gets the notion that he wants to go somewhere?

The government has not hesitated to crack down on industrial polluters. But not the driver. He gets *carte blanche*.

CLIFFORD L. GRAVES, M.D.
La Jolla

The Present and Future Role of Blue Shield

CARL E. ANDERSON, M.D., *Santa Rosa*

MANY PHYSICIANS, concerned leaders of the public and government officials are now raising questions concerning the purpose and the need for Blue Shield.

Most knowledgeable people will agree that Blue Shield has done a reasonably good job in the past.

- It has prevented a complete governmental take-over of the financing and provision of medical care.
- It has made necessary medical care available to large numbers of low income families.
- It has been a mechanism for experimentation with coverage of previously uninsured medical services.
- It has provided the opportunity for medicine to establish standards for medical care prepayment.
- It has developed the experience with underwriting of medical care which has done much to make possible the growth of the entire health insurance industry.

Despite this impressive record, various factors have recently created uncertainties in the minds of physicians regarding the usefulness and desirability of Blue Shield; for example: extension of government into the financing and regulation of medical care; availability of other forms of insurance and prepayment; pressures to expand group practice; emergence of Foundations for Medical

Care; inflation in the costs of providing medical care; the "usual and customary" charge concept; increasing burden of paperwork; and the decreasing freedom of physicians to practice as they have in the past.

Many doctors now look upon their own Blue Shield plan as another "repressive regulatory mechanism" which requires paperwork, frequently reduces fees, and occasionally denies payment because services are considered inappropriate or unnecessary. Blue Shield plans that are "carriers" for Medicare and Medicaid are accused of having "sold out to government." The reasons for a member physician to assure his services to a patient for a fee determined by "someone else"—even though that fee is "usual and customary"—have become blurred amidst distortions of these concepts in governmental programs. The fear of rigid fee schedules, fixed by government at inadequate levels, is ever present. Why then should the physician submit to the "service concept"? Why should he belong to and support Blue Shield?

For the profession, many of the advantages of Blue Shield are "intangible" and accrue to the profession as a whole rather than to the physician as an individual. This is perhaps the reason that many physicians, harassed as they are by multitudinous irritations, are not continuously conscious of what Blue Shield does for them.

Direct payment to the physician by Blue Shield provides assurance of payment without losses from bad debts and without additional collection expense. Complaints about the amounts paid

The author is chairman of the Board of Trustees, California Blue Shield.

Reprint requests to: 1405 Montgomery Drive, Santa Rosa, Ca. 95405 (Dr. C. E. Anderson).

may be discussed with representatives of the organization who are sensitive to the problems of the physician. Unresolved differences may receive, upon request, review by medical advisors or local peer review committees.

The broad policies of Blue Shield are established by the Board of Trustees composed of physicians and public representatives, all of them elected by the state medical association. Payment levels and necessary controls in privately underwritten programs are approved by the trustees. These payment levels and controls are frequently reviewed and discussed with committees representing organized medicine at all levels. Every year, the House of Delegates of the state medical association reviews the actions of Blue Shield, makes recommendations to the board, and elects trustees. In a real sense, the state medical association exerts a strong influence on Blue Shield.

Through Blue Shield, the medical profession has a tool for experimentation in new and untested concepts of medical care coverage and in mechanisms of payment. At the request of the California Medical Association, Blue Shield pioneered in the development of "usual, customary or reasonable charge" programs, and in the implementation of both the 1964 and 1969 Relative Value Studies in private sector programs. Coverage for newborns from birth, psychiatric care and drug and dental coverages have been other areas of experimentation by Blue Shield. Under consideration for early implementation are experiments with coverage for multiphasic screening, and other selected screening procedures, and optional coverages for group practice plans when approved by the local medical society.

The connotations of governmentally financed programs, with multiple and often changing regulations, paperwork, and other unpleasant concomitants are odious to nearly all physicians. But without the continuous and many-faceted activities of Blue Shield in dealing with governmental agencies, these would be even more odious, even intolerable.

Principles of Negotiation

Blue Shield alone, and at times in concert with representatives of organized medicine, carries on daily contacts, discussions and negotiations with government at all levels on behalf of the private

practice of medicine and the ideals of a free medical profession. These activities are generally unknown to the individual physician. They are rarely publicized and are almost uniformly unappreciated.

In such activities Blue Shield is not playing just a one-sided role in favor of the physician. It is Blue Shield's conviction that the public is best served by a profession unhampered by unnecessary governmental regulations, adequately compensated for the services it provides, and permitted to continue to improve itself and its public services in an environment which fosters and encourages improvement rather than one which is repressive and which tends to stifle initiative and to encourage mediocrity.

Medicine and John Q. Public have no other comparable ally dedicated to the improvement of medical care.

Local Peer Review

Blue Shield is committed to the use of local peer review mechanisms. For the purposes of uniformity and administrative efficiency, guidelines for claims review are developed by physicians and implemented statewide. However, local variations in patterns of practice require that the advice of local physicians be obtained in unusual cases. They also help in identifying local characteristics of medical practice which may vary from the guidelines that are broadly applied. Blue Shield not only prepares factual information for local peer review in specific cases, but at the request of a local committee makes available statistical information to help the local group evaluate local practice patterns by comparison with other areas and with statewide experience.

As a result of its computerized claims processing of both private and governmental programs, Blue Shield, at the state and national level, has an enormous accumulation of information which permits evaluation of a wide variety of factors relating to costs, utilization and the influence of variations of program characteristics on the patterns of medical care. This information is continuously evaluated by Blue Shield, and can be made available to medical associations wishing to evaluate their own performance.

Leaders in labor, government and industry are concerned over the rising expenditures for medi-

cal care (which they often mistakenly equate with the increase in charges for units of service). They are often unaware of, or unwilling to recognize, the extensive controls exercised by Blue Shield to conserve the funds entrusted to it. Blue Shield is sometimes alleged to be merely a "conduit" for the passage of money into the hands of physicians. Since most Blue Shield plans are governed at the policy level by physicians, they are said to be incapable of exercising significant controls over either the levels of fees paid or the quality of services for which payments are made. Why then should Blue Shield plans be entrusted with the billions of dollars they receive and pay out each year?

Blue Shield was founded to serve but one master—the public—in matters of medical care. From the foregoing it is evident that Blue Shield, in the conduct of its services to the public, must be accountable to and responsive to the legitimate requirements and concerns of physicians on the one hand, and to the public on the other. At times the requirements of the public sector seem to be at variance with the requirements and concerns of the medical profession. Blue Shield, therefore, must walk carefully to keep these forces in balance.

Continued viability for Blue Shield thus requires that it produce advantages for both the public and the medical profession while exercising reasonable controls to decelerate inflating charges and to avoid payment for services which, after careful professional review, are found to be unnecessary or of unacceptable quality. It is fortunate that most practicing physicians recognize that reasonable controls benefit rather than harm the profession. In fact, most of the controls under which the profession now functions—licensure, certification and accreditation—were devised by the profession for its own improvement and to protect the public.

Blue Shield provides unique advantages to the public and to government.

For the public:

Blue Shield provides, nationwide, the opportunity for individuals and groups to prepay for the necessary services of physicians and, through cooperative arrangements with Blue Cross, for most of the cost of medical and hospital care.

This coverage is available in every state and in some foreign countries.

Through its participating members, Blue Shield assures the patient that member physicians will accept the amounts paid by Blue Shield for covered services as payment in full.

It assures the public that the greatest possible percentage of the premium dollar is returned in benefits to the subscriber. Blue Shield's non-profit status and consistently low administrative cost provide this assurance.

The public has the confidence that the medical profession, expressing itself through Blue Shield, is more interested in providing care and assuring its services than it is in charging "what the traffic will bear."

For government:

Blue Shield provides a unique channel of communication with the medical profession and the opportunity to receive the benefit of professional opinions and advice in the administration of government-financed health care plans.

In using Blue Shield as a carrier or fiscal intermediary, government also receives the benefit of more than 30 years' experience in administering health care prepayment to over 70 million subscribers, along with private sector efficiencies and economies resulting from this vast experience.

Conclusion

Blue Shield faces the future after more than 30 years of growth and accomplishment in which it takes pride, though it is far from satisfied. It is acutely aware of sharp criticisms by physicians, labor, management and government. These criticisms are valid, in some instances. More often they appear to be based upon misinformation or lack of knowledge of many of Blue Shield's activities.

Analysis of Blue Shield's present functions indicates that it offers many unique advantages to the public, to government and to the medical profession. To provide these advantages in a complex and rapidly changing environment, Blue Shield must continue to improve its traditional functions, pursue effectively the activities it has more recently embraced (particularly in the administration of governmental programs), and

move into new areas of experimentation and medical care administration.

So in the future Blue Shield must:

¶ With the support and understanding of the medical profession, maintain and expand the service concept for the prepayment of medical care services.

¶ Strive to achieve an even larger role in the administration of medical care programs financed by government.

¶ Continue experimental activities to extend prepayment coverage into new areas of medical services and new "delivery systems."

¶ Expand its support of local and statewide peer review activities. (Ideally this should be done in close cooperation and coordination with Blue Cross.)

¶ Continue to expand its capabilities to analyze its enormous data resources to provide reliable evaluations of factors influencing medical care.

¶ Continue its "buffer role" activities between the profession and government in order to pre-

serve the benefits to the public of a free and self-regulated medical profession.

¶ In cooperation with the medical profession, continue to develop and apply reasonable controls to provide justifiable levels of payment for appropriate services rendered to subscribers.

¶ Be alert and responsive to opportunities to cooperate with other private and public agencies through which segments of the public might gain greater accessibility to and more effective use of available medical care resources.

Blue Shield has an unparalleled record of public service—achieved through its cooperative arrangements with the medical profession. It affords unique advantages to the public and to the profession. Within Blue Shield there are capabilities for experimentation, evaluation and change, which if appropriately used could achieve enormous gains in the future of medical care services. Blue Shield needs and deserves the support and confidence of the public and the full endorsement and cooperation of the medical profession.

BENIGN POSTOPERATIVE FEVER

"A diagnosis of benign postoperative fever is presumably made by exclusion. Certainly no one would make this supposition without trying to exclude other causes. It is described by Roe who states that it is seen in association with the intraoperative or immediately postoperative drop in temperature to 96 or 97°F. The rise in temperature follows rather quickly and then disappears within 36 hours and is not associated with any of the findings of other causes of fever. Roe's belief is that it is due to a temporary derangement of the limits of the temperature-regulating mechanism, possibly as a result of the effect of the anesthetic agent on the hypothalamus. . . . I don't think one makes the diagnosis except as a matter of medical curiosity when one has excluded other factors. There's no treatment for it.

"The substantiation for the concept (and it's not just a will-o'-the-wisp idea) is that one can demonstrate it in an animal, by the administration of anesthesia, as a small transitory drop lasting only a few hours and then a rise following anesthesia. If you prevent the drop in temperature by warming blankets or insulation, you don't get a rise in temperature following the administration of subsequent anesthesia. Hence this is looked upon as a physiologic response to the stress of anesthesia or to the stress of anesthesia plus surgery."

—ALLAN D. CALLOW, M.D., Boston
Extracted from *Audio-Digest General Practice*, Vol. 18, No. 3, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057

The Medical World of Frederick the Great

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THE TURN of the seventeenth century marked the beginning of an era that saw a hitherto insignificant Prussia win a seat in the concert of the great powers in Europe. Two monarchs of extraordinary stature, the Hohenzollern kings, Frederick William I and his son and successor, Frederick II, accomplished this feat; and for better or worse, the continent, in fact the world, had to reckon with this event in the centuries to come until our very own day.

To use present-day parlance, both sovereigns in their adolescent years had been "anti-establishment" and found themselves in a deep "generation gap" with the way their elders were conducting the business of royal ruling. Frederick William I was a man of incorruptible righteousness and of a practical Christian piety. He was, in modern terms, the "square" incarnate. Appalled at the waste and extravagance in the regime of his father, King Frederick I, and dismayed by malfeasance and overt defalcation of his father's ministers and public servants, from the day he was crown prince, Frederick William had resolved to change it all. And change it he did. On his ascent to the throne in 1713 the watchwords in Prussia became husbandry and soldiery, thrift and service. The country's military and financial weaknesses his father had left him were transformed by Frederick William's passionate devotion to the army and his unremitting dedication to the ex-

igencies of civil administration into the characteristic features of the Prussian state: efficiency, organization and discipline. Frederick William I, generally known as the "soldier-king," was actually Prussia's greatest ruler in home affairs.

Nor did King Frederick William allow for deviations in the rigorous demands of the monarchy. It was here that Crown Prince Frederick, his son and heir, came to grief. Contrary to his father's wishes for a strict military and sober Protestant upbringing, he showed preponderant intellectual leanings, a love for music and literature, and adopted freethinking philosophy. Political aspects finally entered the tension between father and son and came to a head when in 1730 the crown prince made an abortive attempt to flee the country. The king reacted with utmost severity to what he considered desertion from the army. He stripped his son of his military rank, had him imprisoned and made him watch from the window of his cell the execution of his friend, Lieutenant von Katte, a co-conspirator in the escape plot.

If ever educational "shock treatment" succeeded, it was in the case of Crown Prince Frederick. He submitted to his father and completely changed his attitude toward the claims of his prospective royal duties, served in lowly positions in a provincial administration and, in 1733, married for political expedience an unloved Princess of Brunswick-Bevern. This unhappy bond with a goodhearted but unattractive and intellectually barren partner remained childless.

When Frederick II succeeded to his father's crown in 1740, he looked back upon seven delightful and rewarding years in his retreat at the castle

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of Rhcinsberg, where he had devoted himself to extensive reading and systematic studies in French literature. In correspondence with Voltaire he had acquired a complete mastery of French, which became a natural means of expression to him. His rare attempts at his native tongue resulted in paragons of ungrammatical German, of which the hand-written letters to his valet, Fredersdorff, furnish touching proof.¹

The ideal of government became for Frederick an "enlightened" but "absolute" monarchy serving the welfare of the people under the ruler's sense of responsibility. He immediately put his enlightened and humane principles into practice. Exiled scholars were recalled, torture was abolished and penalties for crime were mitigated. Lavish patronage was extended to music and the arts, and an opera house was built in Berlin. This *roi philosophe* held court among persons with outstanding minds from all over Europe; but it soon became clear that he was also a statesman and soldier and in no way planned to inaugurate an easy-going regime.

Within less than eight months after his accession to the throne, he opened *Blitzkrieg* against Maria Theresa of Austria and secured by a lightning campaign what at best were doubtful dynastic claims on Silesia. It was a purely aggressive war; and so was its continuation a year later, when some of Frederick's most notable victories in the field finally gained the coveted territory. Yet for several more years the fighting went on with changing fortunes of war until, in 1745, Frederick prevailed and hereafter attained his subjects' designation of "the Great."

In the subsequent decade of peace, 1746-1756, a matured king devoted all his energies to the service of the state, which became the religion of this mocking skeptic. On the foundation of his father's administrative organization, the famed *rocher de bronze*, progress was made everywhere, commerce and industry thrived, the population grew and every family had its "chicken in the pot on Sunday." In his rococo palace the royal "philosopher of Sans Souci" found his only relaxation in learning, in literature, in flute-playing and in collecting art. Around him was gathered a circle of literary friends; and Frederick's own literary work reached its height in his *Histoire de mon Temps*, vastly superior in style, clarity and political judgment to most other contemporary academic writings.

As he was certain that Maria Theresa would never be reconciled to the loss of Silesia, Frederick stayed prepared for war continuously. When this Seven Years' War came in 1756, Prussia was able to survive politically intact by her king's unbending will and his stoical indifference to adversities. Yet the country was left in utter ruin. Its reconstruction, Frederick's greatest peacetime achievement, equals his military performance in the Seven Years War. When "Der Alte Fritz" ("Old Fred") died in 1786, he left a prosperous land with expanded territory and rich new provinces, with many reforms and projects of great promise. He had made Prussia a model state of "enlightened despotism" admired by her contemporaries. But the system was already outmoded at the time of his death because only the "omnipresent" king knew how to control it. To admit this does not diminish the significance of this monarch's creative achievement or of his personality as a statesman. The intensity and the self-discipline with which he strove for harmonious solutions of his political problems assured him of true and lasting historical greatness.

A Facet for All Historians

It is no longer only the conventional historian who can unfold the full many-sidedness of Frederick the Great's extraordinary personality. The facets that sparkle in the life and achievements of Prussia's greatest king cast light on a multitude of aspects and yield important material for a variety of specialist studies in the history of politics, of military history, of sociology, philosophy, literature and even of medicine. Probing in the last-named field, I arrived at startling realizations of general interest which prompted me to prepare this paper on the relations of Frederick the Great to the medical world of his times, both with regard to his personal medical history and to his influence on the healing arts in general.

Frederick himself had more than his full share of health failings and sickness, probably more than the majority of his fellow humans. Among the causes may have been the enormous physical and mental strain his royal calling imposed upon him. We possess contemporary accounts by two of his personal physicians, Drs. Selle and Zimmermann.

Dr. Selle, in his "Case history of his majesty the King of Prussia, Frederick the Second,"² describes

the monarch's terminal days of suffering with only a few remarks about his earlier state of health. The essay is addressed to the medical profession, a matter-of-fact, objective and totally unsensational postmortem of little interest to the nonmedical reader. The fact that Selle's account never attempted to relate the king's personality with his illness may be why Selle's report has never become widely known.

In contrast, the writings of Dr. Johann Georg Zimmerman found extensive dissemination among contemporary readers. His book, published in 1788, is entitled *Über Friedrich den Grossen und meine Unterhaltungen mit Ihm kurz vor seinem Tode* (*On Frederick the Great and my conversations with him shortly before his death*).³ Zimmermann had been called to the bedside of the ailing king as a consultant of international renown. He was a student of the famous Albrecht von Haller, whom Frederick profoundly admired. As in most of his literary and medical works, Zimmermann had no intention of producing a treatise for his colleagues; he wrote for the reading public at large, who wanted sensation and human interest in their stories.⁴ In such writing he transgressed beyond strictly medical aspects and often disregarded professional discretion—by recounting, for instance, that Frederick as crown prince had contracted venereal disease on a visit to his paramour Orzelska in Dresden, a statement which actually has remained unverified. As a result Zimmermann incurred severe criticism, in his own time and later, and became a rather unpopular figure. In many respects he may be compared in our day with Lord Moran, who published the case history of another illustrious patient, Winston Churchill, who had been in his medical care. There are, however, exceptions in the large chorus of critical opinions about Zimmermann, and one was expressed by none less than Goethe in his fifteenth volume of *Dichtung und Wahrheit*, where he stated that vanity as such was never offensive to him.⁵ Goethe was favorably impressed by Zimmermann's elegant and worldly deportment and wrote on several occasions about this strangely arrogant physician. Equally impressed, by the way, was Goethe by Zimmermann's most venerable patient, Frederick the Great; after reading his works, he said on October 25, 1788: "*Es ist doch etwas einziges um diesen Menschen*" ("There is truly something unique about this man").⁶

There was no lack of competent physicians in eighteenth-century Europe. Many practitioners had studied with outstanding teachers at home or abroad. Besides Albrecht von Haller, who taught at the newly founded university in Göttingen, and at others, the most renowned of that period was the Dutch internist Herman Boerhaave (1688-1738) at the University of Leyden. He was the first to introduce clinical instruction at the patient's bedside and to establish a teaching hospital, where he took his students on medical rounds to observe the daily changes in the patient's condition. His literary legacy unfortunately never approached what he had done for his patients and students, who flocked to him from all over the world. Haller, his most prominent pupil, called him "the General Teacher of all Europe," and his fame had also reached Frederick the Great, who kept constantly abreast of all intellectual and medical currents of his time. He ordered the doctors in his employ to sit down and study their "Boerhof" (sic), and he also probably knew that in 1745 his old adversary, Maria Theresa, had called a Boerhaave pupil, Gerard von Swieten, from Leyden to the famous Vienna School of Medicine with the task of placing public health service on a new and better footing.

If we examine the efficacy of medicine in the eighteenth century of Frederick's lifetime, we must bear in mind that by present standards the doctor's therapeutic armamentarium was exceedingly meager. Diagnosis was made by establishing the rate of the pulse and by gauging the body temperature (fever was judged by complexion of the skin and delirium, not by thermometer readings, for the clinical thermometer was not in general use until James Thompson established the absolute scale in thermometry in 1849). A further diagnostic criterion was urine examination. Few diseases were actually known: gout, intermittent fevers (malaria), smallpox, the plague, typhus, dysentery, influenza, venereal disease, hemorrhoids, stones, hernia. Treatment for the last two was operation (without anesthesia or antisepsis, which were not yet known). Venereal disease was treated with mercury ointment and vapors. For malaria there was cinchona bark, also known as Jesuit bark, now known as quinine (because of its effect in malaria cases, it was sometimes also used on all feverish diseases). Smallpox was ever-present and led to the first

attempts at inoculation. In gout the recommendation was a careful diet, abstention from "red meat, wine and high living," for gout was thought to be a disease of the well-born, well-to-do, and it was believed that turning to more frugal habits would be the cure. In the case of the plague, there was only prayer. Wounds, injuries and fractures were treated by surgeons and *Feldschers* (paramedics), who took charge and did the best they could in the circumstances.

Love and Disease

When Frederick II was born in 1712, it was reported to his grandfather, Frederick I, that the infant was fat and healthy. In his growing years the boy had resisted parental advice for physical exercise and was known to have avoided activities involving any physical discomfort. That this contributed to his later corpulence and severe constipation is more than likely. Frederick at the age of fifteen weighed almost one hundred thirty pounds, and early portraits show him as a heavy-set, ruddy-faced youngster. No doubt another contributing factor was his voracious appetite—an appetite he maintained even in later years when his health grew frail and when his physicians would demand a carefully restricted diet. His baby fat vanished after two attacks of what was reputed to be smallpox in 1718 and 1724, and some of his contemporaries described him even then as appearing "oldish and stiff," almost as if he had participated in some wars.

Subsequently there is constant mention of illnesses of Crown Prince Frederick. From time to time he did lose his appetite, became suddenly emaciated and looked like his own shadow. King Frederick William, his father, complained about this to his friend Prince Leopold of Anhalt-Dessau (the famed "Alte Dessauer" who played an equally important role in the lives and reigns of both father and son) and was "afraid of the worst"; in fact, he suspected *Auszehrung*, that is, consumption. Frederick's eldest sister, Wilhelmina, to whom he was always very close, did not share their father's concern for her brother's health. She attributed, perhaps rightly, this delicate appearance to Frederick's longing for a glamorous young woman, the Countess Orzelska, with whom he had fallen in love on a trip to Dresden. Indeed, shortly thereafter the crown prince began to ail with a variety of "nervous"

complaints, occasional feelings of suffocation, sleeplessness and palpitations of the heart, and at the same time he suffered from his most frequent misery, severe gastric colics. It would all add up to a model case of hysteria, or, as it was then called, hypochondriasis; but then it is not impossible that the ground had already been broken for the continuous gastrointestinal difficulties that afflicted Frederick all his life. Another peculiarity also seems to have developed at this time: Frederick's strong inclination to perspire violently. It finally went so far that all his night clothes and bed linens had to be dried before an open fire, summer and winter. As the dating of its first appearance is not totally reliable, this last symptom may also have been a manifestation of the malaria which Frederick contracted during his Rheinsberg days. It was there that he began to take china bark, now called quinine. Because this medicament suppressed his malarial fever, he developed the habit of taking it for any other fever condition that befell him.

Frederick was, in fact, habitually given to self-medication. He also prescribed for others near and dear to him. Inveterate scoffer and skeptic that he was, doctors by and large were quacks to him. The few exceptions included Boerhaave and Haller, whom he knew by their scientific reputations; also Cothenius, Selle and Zimmermann, whom he trusted as his personal physicians. All others he mockingly lumped together as charlatans who undertook to give him lessons, whereas he felt thoroughly schooled in the art of healing. So certain was he of his medical knowledge that he freely medicated and prescribed for his favorite sister, Wilhelmina, and his brother Ferdinand, both of whom lived in a state of chronic invalidism. He also supervised their physicians and had them report to him about the smallest details of their treatment. The same was the case with his erstwhile valet and subsequent councillor Fredersdorff, one of his most intimate and beloved confidants, who was, in Voltaire's words, *le grand factotum du roi Frédéric*. Only here, Frederick's habitual medication of others turned into something of an exchange, because Fredersdorff practiced alchemy and had concocted a number of the elixirs which Frederick took himself and dispensed among his chosen wards. The rare relationship of utter mutual trust between these two men is revealed in their extensive correspondence, which is largely

preserved and full of moving expressions of intense mutual concern for each other's health and well-being.¹

Gout and Hemorrhoids

Frederick's contempt for the "charlatans" finally went so far that he consulted physicians not on what medication to take, but only on how much to take. Yet as time went on, the king's suffering from gout increased markedly. As we learn from his Swiss reader and companion, von Catt, repeated exacerbation of hemorrhoids was another complaint, perhaps more a nuisance than an actual danger. The combination of previous illnesses, especially the frequent gastric colics, the severe chronic constipation, the king's usually sedentary way of life and his predilection for culinary excesses, would seem to form a logical background for the two principal ills which plagued Frederick to his dying day: gout and hemorrhoids. He also appears to have suffered from asthma, although it is impossible now to ascertain whether this so-called asthma was the allergic and emotionally conditioned disease that is now known under the name "bronchial asthma." Or were the repeated attacks of inability to breathe not in fact symptoms of congestive heart disease, angina pectoris or emphysema, none of which were then recognized as disease entities? At any rate, these attacks of asthma never lasted more than a few days and were generally amenable to the friendly assistance and harmless medications of his currently favored physician. All in all, the desperate degeneration of Frederick's health from the time he entered his thirties was quite in contrast to the healthy beginning of his life. It must still remain a major miracle how he was able, in his condition, to perform the tasks—at times superhuman—he had set for himself. He was not a well man.

Things of the Mind

So much for the somatic aspects of the medical history of Frederick the Great. Concerning the psychological side, it is small wonder that the mental and emotional functioning, or malfunctioning, of this exceptional personage became a choice subject for psychological investigation, both professional and amateur. Inasmuch as the best diagnostic methods — personal observation and interrogation—are no longer applicable, the

probing is of necessity confined to the interpretation of literary material. It therefore follows that any findings must remain speculative.

The most sweeping contemporary opinion was propounded in 1744 when, during a stay in Bad Pyrmont, a spa that Frederick used to visit for his health, the various royal physicians agreed that the king was suffering from "a choleric-melancholic temperament with a hypochondriacal affect on his body and soul." Von Catt, the king's reader, also speaks of observing frequent spells of melancholy, which occurred with aggravation of hemorrhoidal pain.⁷ There is, however, no indication that this depressive condition had ever taken threatening or debilitating forms. It seems to have been Frederick's natural reaction to mental or physical torment, of which he had quite a measure, and this reaction apparently remained ephemeral. Equally transient remained his not infrequent threats of suicide, of which the earliest fell in the time of his engagement and enforced marriage with an unloved and intellectually inferior bride. His feelings about the whole matter of his marriage he expressed, somewhat impolitely, in the statement that he would have preferred a prostitute to a pious and unintelligent lady. At all times he clung to this life-long habit of voicing threats of suicide either orally or in letters to his friends; but even in the most desperate situations—and there were quite a few—he never seemed to have come close to carrying out such threats. He died of natural causes at the age of 74, unless we call habitual overeating a mode of slow suicide. On the subject of overeating, I wish to quote the all-knowing Dr. Zimmermann, who told of one occasion when he visited the king:⁸

At three in the afternoon I found the king in the most painful situation: every thing was changed and become worse. When in good humour, he had taken his [medicine of] dandelion and drank coffee: after this, he had applied, from half after three in the morning till seven, to public business. Great part of the morning he had spent in eating; for as soon as I left him, a plate of sweet-meats, composed of sugar, whites of eggs, and cream, had been brought him, one of which I ate, and found the cream very sour. His majesty ate the whole plateful for his breakfast; and afterwards strawberries, cherries, and cold meat. At eleven his servants found great difficulty in getting him on horseback. He remained there three hours, in the

great garden of *Sans Souci*, galloped almost the whole time, and returned very much weakened and exhausted. When he sat down to table he had no appetite; and immediately after dinner he was seized with a vomiting.

[On the next day] the king was much better than he had been the day before, after dinner; he however complained of a constriction and heaviness at his stomach. I advised him to take a dose of his digestive powder, which was his favourite remedy.

At three the king was again attacked by a colic, the consequence of indigestion; and he was in very bad humour. At dinner he had eaten plentifully of fresh eels, and yet he ascribed his colic to dandelion. He railed therefore against *Mr. Physician* and the dandelion.

For several days successively the king had taken some of his dear digestive powder; and afterwards rhubarb, and glauber salts, which I thought much more proper. Yesterday evening several strong stools had dispelled for a moment all his bad humour. "A new remedy," says his majesty, "has just arrived, which I mean to try at noon; this remedy," added he, "is fresh herrings." I congratulated his majesty on his new remedy, and begged him not to forget rhubarb and glauber salts, after which I was dismissed at the usual hour. After dinner, the king was not so well as he had been in the morning; but he behaved with much politeness.

Of Bed and Battlefield

A select field for speculative historical analysis is the investigation into the question of Frederick's standing in sexual matters. Of factual information we have his own statements: in 1771 when he recalled a favorite, but unnamed, paramour and said, "I remember with pleasure the wonderful moments which I spent in the arms of a young girl. She was not insatiable, but said with a certain degree of gentleness: 'My dear little hero, if you make yourself sick you won't be able to carry on war.'"⁹ It is not known to which of his two girl friends this episode refers—whether it was to a certain Formera, who was said to have been as "beautiful as the graces"; or to the Orzelska who was described by a contemporary, Pöllnitz, as a woman "of fine figure who had something grand in her air and carriage and the prettiest humor in the world." A further remark by Carlyle about this Orzelska, the second enamorata of Frederick the Great, is rather telling: "She often appeared in men's clothes, which became her very well.

People also said she was extremely openhanded." This last attribute differentiated her thoroughly from her royal friend, who was famous—or infamous—for his caution about spending money. The revenues from the state of Prussia were at times remarkably meager.

We also have witness from the indefatigable Dr. Zimmermann, who claims possession of reliable information that the crown prince had relations with a certain number of courtesans and on one such occasion contracted a venereal disease shortly before his marriage in 1732.¹⁰ This accident alone, but especially combined with Frederick's total indifference—possibly even aversion—toward the bride chosen for him by his father, could very well be the explanation for the childlessness of their marriage. Yet nobody will ever know for certain, because factual evidence has never come to light.

Nor was reliable proof ever offered for allegations that Frederick had homosexual leanings. There are speculations galore on this subject. They customarily fall back on references to the extensive writings of Liselotte, the witty and gossipy Princess-Consort of the Elector of the Palatinate.¹¹ For a lady of her rank and standing, she really possessed quite an amazing store of intelligence about contemporary sexual mores in the barracks and the camps in the field, to say nothing about her delving into the apparently rampant homosexuality at miscellaneous courts on the continent. The imputations of her sharp pen, which spared not even the highest and even pointed unforgivingly to personages like King Louis XV of France and the famed Austrian field-commander Prince Eugene of Savoy, and others with whom Frederick was well acquainted, would hardly stand up in any court of law as evidence of his homosexual involvement. Equally unsupported remain Voltaire's stigmatizing utterances on this theme, which came at a time when the king's lifelong friendship with the great philosopher had cooled. Without any apparent value, even as innuendo, this whole speculation may therefore be put *ad acta* as old wives' tales.

In a Word, Porphyria

In the light of present-day medical views, it would not seem too far-fetched to consider the variety of ailments that plagued Frederick the Great, not in their multiplicity, but simply as the

symptoms of one disease. This disease, diagnosis of which appears likely, is a metabolic nonsex-linked hereditary dysfunction, not very frequently found, called porphyria. Such a diagnosis would be supported by practically every manifestation in the total picture of the king's illness, all of which are known to be typical symptoms for this disorder. Particularly his chronic gastric colics and violent sweating, headaches and accelerated pulse, painful limbs and dark red urine (which, incidentally, accounts for the name of this disease), as well as ascites in his later years, and the weakness, occasional convulsions and depressive states that seized him from time to time. Another strong hint for the possible existence of porphyria would come from Frederick's genetic background. He was a descendant of the houses Hohenzollern and Hanover and a blood relation to George III of England, the "last king of America."¹² According to recent medico historical research, it is now assumed that George was a sufferer from porphyria,¹³ which is an inheritable disease and may have affected many members of these large families.

We have herewith arrived at the conclusion of the medical case history of King Frederick the Great. It now remains to take a look at this unusual monarch's attitude toward the medical questions of his day in general and his influence on them.

As Frederick II continued unchanged the strong military policy of King Frederick William I, he fully realized, like his father, that success on the battlefield would never be derived solely from the drill of the army and the tactics of his dreaded oblique line of battle. He was always aware of the signal importance of troop morale and its dependence on the concern of the leadership for the individual soldiers. Frederick made sure, therefore, that every last man received his pay and rations with the utmost punctuality, as the old marching song "Fridericus Rex" approvingly acknowledged. He also took care that the wounded and sick were not left to their fate. It appears, therefore, that it was Frederick the Great—not, as has long been assumed, Napoleon's Baron Larrey or the Americans in the Civil War—who conceived the idea of and introduced field hospitals and mobile (the so-called "flying") ambulances.¹⁴ All the minutest details for the military medical

system were worked out and supervised by the King himself, and he commissioned Dr. Fritze as superintendent of all army hospitals. Evidently Frederick had made a good choice, because Dr. Fritze, in 1780, very soon after his appointment, published a remarkably intelligent analysis of the Prussian army medical system.¹⁵ Nevertheless, it was actually the king who had to carry through his own reformation of the military health system, because Dr. Fritze died very shortly after completing his book.

The effective systematization of military medicine was difficult to carry out in the midst of war; hence Frederick had to postpone his reorganization until the wars had ended and actually devoted much of the final years of his government to the reforms of the military medical service. There were many problems that had to be settled. One was the hiring of a group of well-schooled physicians—"the young *Aesculapes*," as he called them—as suitable wartime staffs for the army hospitals and the troops. As for this appointment of physicians, the King decreed on December 30, 1780, that the medical faculty in Berlin was to maintain in peacetime a sufficient number of well-trained physicians for field and hospital duty. He ordered that doctors be selected "who had proved their mettle and who were better than those in the hospitals during the last war." And, furthermore, Frederick the Great, whose nature and government had always excelled in almost exasperating parsimony, instructed his much-admired personal physician, the Privy Councillor Cothenius, to figure the cost of a well-run field hospital, as well as a perfectly stocked field-pharmacy, both of which were to be planned with all perfection—and this time regardless of the expense it might involve. As was to be expected, with Frederick's careful planning the Prussian military medical service could serve as a model for all armies.

Public Health and Hygiene

But the King's concern for the organization of military medicine was vastly overshadowed by enormous problems relating to public health and hygiene in general. They required his constant intercession. Chief among these were the frequent outbreaks of contagious diseases, which ravaged not only the armies but the population as a whole. Plague, cholera, smallpox and typhus were the most frequent of these epidemics and

they usually took a dreadful toll. The eighteenth century was totally ignorant of any theoretical knowledge concerning the mode of contagion; nevertheless, intelligent use was made of quarantine whenever it seemed indicated. Frederick's attitude in these emergency situations was as remarkably enlightened as were most measures of his long reign. This is illustrated by one of his edicts in relation to quarantine intended to stem epidemics which clearly shows his awareness of the psychological side-effects. His order was never prematurely to disturb the flow of commerce, because rumors of epidemics often were nothing but false alarms sounded by the enemy so as to demoralize the troops and the people.

Beyond measures to prevent their spreading, Frederick actually attempted to disarm two of the most devastating diseases of his day, for which so far neither cure nor prevention had been discovered. These diseases were *Tollwut* (or rabies) and smallpox. No effective means of averting rabies existed before Pasteur's masterful discovery, although almost every imaginable nostrum was tried on the stricken. Rabies, or hydrophobia as it had been called in earlier times, ran unchecked through the human and animal population, just as it had since time immemorial and with a vastly higher frequency than in recent days, when the incidence has been kept low by the inoculation of dogs, which practically excludes from the chain of infection the once most frequent carrier. The other dreaded and fearsome disease was smallpox, which was rampant in the days of Frederick the Great and which he had contracted in his childhood. Smallpox, in fact, unlike other diseases which somehow seemed to respect the rich and the well born, was violently dangerous to all men from the common soldiers and workmen to the clergy, nobility and even the royal houses. There was scarcely a family in seventeenth and eighteenth century Europe which had escaped the loss of a child, or several children, to this disease, which, if it did not kill, left its victims cruelly disfigured by irreparable scars.

Smallpox Inoculation

The dread of smallpox was international, and it was the first disease that had ever given rise to attempts at preventive medicine. The earliest records on the prevention of smallpox come from China in the twelfth century, when *inoculation*

(to be sure, not vaccination) was practiced by applying ground and pulverized scab from the skin of victims of light cases of the disease. This pulverized matter was blown into the nostrils of the healthy child—or the infant was swaddled in a blanket over which smallpox dust had been scattered. In many of these and other variations of exposure to the disease, the inoculated patients would contract the infection, generally in a light form, and forever remain immune to reinfection. The Chinese method was adopted by other Asian peoples and became widespread to many parts of Africa and Asia Minor, where Lady Mary Wortley Montagu, the wife of the English ambassador to Turkey (1718-1721), observed this practice of inoculation.¹⁶ Not only was it more or less possible to regulate in this fashion the severity of the disease and to avoid many fatalities, but also to keep in check the very disfiguring scars (of special importance in Turkish harems). So impressed was the ambassador's wife that she practiced this form of inoculation on her children and brought news of it to England, where it came into great vogue until it was later replaced by Jenner's discovery of vaccination, the method of inoculation with cowpox. The Swiss physician Theodor Tronchin and the Tuscan Angelo Gatti were especially influential in popularizing the method on the European continent. Frederick II, of course, kept himself completely informed on this new prophylactic measure. In order to make Prussia safer from smallpox, he commissioned several English physicians to carry out inoculation in Berlin and to train Prussian doctors in this method. He was utterly enraged—in fact, it was said that he “hit the ceiling” (“*er ist an die Decke gesprungen*”)—when he heard that the French clergy objected to this prophylactic measure after they had been consulted by the Parliament in Paris. It was the famous encyclopedist d'Alembert who had kept Frederick the Great informed on these developments. In fact, the French opponents to inoculation might have been victorious in their conservative attitude had it not been for the intercession of the leading French intellectuals, including d'Alembert, Voltaire, La Condamine and the above-mentioned Dr. Tronchin, all of whom were vociferous defenders of the new practice of inoculation. Since these men were close friends of the Prussian king, it is scarcely to be wondered at that their point of view was eagerly adopted by Frederick the Great. The history of Frederick's friendship

with Voltaire is well known. Dr. Tronchin was physician-in-ordinary to the royal house in Versailles and enjoyed Frederick's absolute confidence. Tronchin was even called to the bedside of the ailing Prussian Prince Ferdinand. For d'Alembert King Frederick II had very important plans. He hoped to be able to persuade the French scholar to become the successor to Mauteruis and to take the presidency of the Prussian Academy of Sciences. And even though d'Alembert did not accept this appointment, he became in fact the unofficial president upon whose opinion King Frederick depended for all his scientific decisions.

By far the majority of the physicians in Berlin were opposed to the practice of inoculation. Indeed, in the political correspondence of Frederick the Great there is a letter from a physician in Berlin which reports that among the local physicians "there are not more than three who are in favor of it [inoculation]." In fact, even Frederick's personal physicians, including Dr. Selle, were "declared enemies" of this new practice.

While in Berlin and Paris the practice was slow in gaining proponents, there was much activity in London, where inoculation was performed widely. Since for that operation the skin was opened by means of the lancet, it fell to the surgeons to practice this operation. Frederick the Great became aware of the English medical activities through the reports of his ambassador in London. From this we gather that more than two centuries ago the diplomats were commissioned (like the scientific attachés of the American diplomatic service) to report on scientific and medical innovations.

In 1766 Berlin was visited by an especially severe smallpox epidemic which gravely affected several of Frederick's close relatives. The King requested his ambassador, the Count Maltzan, to make inquiries from the London surgeons who practiced this operation as to whether they might be able to send several of their disciples to Berlin in order to carry out inoculation and to instruct Berlin physicians in this practice. Although generous provisions had been made for the remuneration of the English specialists, the two men proved to be rapacious and made such extravagant demands that the King had them returned to England.

This unfortunate experience, however, did not discourage the King altogether from trying his luck with another English specialist. He began negotiations with Dr. William Baylies, who had settled in Dresden in order to introduce the practice in the Kingdom of Saxony and who was much admired for his tact and skill. Just when Dr. Baylies had responded to King Frederick's summons and arrived in Berlin, Frederick was informed that the Russian Empress Catherine the Great was about to have herself inoculated in order to try this new treatment on herself and also on her son, Paul, the successor to the throne. Frederick believed that inoculation was beneficial for children only, and potentially harmful to adults. He tried his utmost in letters to dissuade the Russian empress from the dangerous experiment. His efforts remained in vain. As for his own person, he absolutely declined to have himself inoculated without knowing that the attack of smallpox which he had suffered as a child would forever protect him from a recurrence of this disease. Even Dr. Baylies' international acclaim and the widespread use of inoculation in other countries did not allay the antagonism of the Berlin physicians. They used every conceivable ruse to get rid of Baylies and to prevent the introduction of inoculation. Nevertheless, Baylies' activities were so successful that he accepted the King's invitation to take permanent residence in Berlin. Thus Frederick the Great had succeeded in introducing the first all-important public health measure in the kingdom of Prussia.

Medical Treatment of Prostitutes

Other public-health measures of the King pertained to the control of vice and the possible limitation of the spread of venereal disease through prostitution. Specially suited women were employed to police the prostitutes. Anyone apprehended plying her trade was delivered by them to the abhorred *Spinnhaus* (Spinning House) in Spandau near Berlin, where she was given time to reflect on the evil of her ways while busy spinning wool for the Prussian cloth manufacture that had been thriving since its introduction by Frederick's father, King Frederick William I. Any who had venereal infection, however, were turned over to the famous Charité hospital in Berlin, which had been opened in 1710 by Frederick's grandfather, King Frederick I. Here they were subjected to mercury treatment and not released un-

til they appeared cured. In the archives are a number of discharge slips of cured prostitutes that testify to the prudence of this regulation.

Frederick's interest in the Charité and his feeling of responsibility for it had always been strongly marked. His usual well-known restraint in expenditures notwithstanding, he raised the royal appropriation for this institution to 40,000 *Thaler* annually and developed it into one of the foremost teaching hospitals and centers of medical education. The king himself, in the beginning, examined the credentials of the staff members and made the important faculty appointments in person. Although the hospital initially did not have university status, the leading positions in the Charité carried the title "Herr Professor." In making his selections for the teaching body, Frederick preferred former students of the famous Albrecht von Haller, and thus eventually all the important positions at the Charité were filled with men who had acquired their medical knowledge from Haller at the University of Göttingen. In this connection, it will be of interest to mention that the first experiments for the therapeutic use of oxygen, which had just then been discovered as an element, were made at the Charité upon the suggestion of Frederick the Great.

Considering the multitude of problems almost beyond imagination that descended upon the King at all hours, it is truly amazing that he was able to develop both an ardent interest and a well-founded knowledge of medical science and its ancillary disciplines. Anatomy especially he studied with the dedication of a first-year medical student, proclaiming that no one could possibly aspire to be a good physician and surgeon who was not thoroughly conversant with the anatomy of the human body. It is interesting that although he sponsored the anatomical department of the University of Berlin and concurred in the department's postulate of using human dissecting material, he made it unmistakably clear that under no condition was his own body ever to be used for anatomical studies.

Home-Grown Drugs Favored

Frederick read most of the contemporary medical journals, and whenever an article struck him as pertinent to his own health or that of his ailing brother and sister or any other patient about whom he was concerned, he would cut it out and

send it to the attending physician with the request that he treat his patients accordingly. He furthermore collected samples of various vegetable or mineral drugs that came into his possession and requested that they be analyzed by his physicians and that a determination be made of their value in certain diseases. A number of such royal missives to various doctors have been preserved, and it seems that they were not always taken by the recipient with unrestrained enthusiasm. The king's respected physician-in-ordinary, the Privy Councillor Cothenius, for instance, reported to His Majesty on one occasion that a Brunswigian balsam, sent to him with the request for analysis and evaluation for the treatment of pellagra, consisted only of volatile and bad smelling uric acid and some other sour and pitchlike component. He said that when in some cases he and other physicians had applied it to old and hardened gouty swellings, the balsam had some effect in the beginning of the treatment, but that was all. Frederick, in keeping with his mercantilist view in economic questions, always had domestic remedies given preference over foreign imports when they proved adequate. He forbade the taking of Vichy water from France instead of the waters from various Prussian spas because of the cost of transportation and customs duties on the former. He himself, throughout a long life of suffering, was content with the waters of Bad Pyrmont and other domestic spas which were reputed to be of help to sufferers from gout.

Besides the aspects of clinical medicine, Frederick also involved himself in the theory of the medical and natural sciences on an international platform. Foremost among the theoreticians with whom Frederick established close contact was Lazzaro Spallanzani, a professor of biology at the universities of Modena and Pavia who had made fundamental experiments on fertilization and conception. His most important work was his attack on the theory of spontaneous generation in 1765, and he became famous for his researches on original creation and infusoria. Of equal importance were his studies on the regeneration of animal tissues and the circulation in embryos and cold-blooded animals. Spallanzani was greatly impressed by the interest of Prussia's intellectual king and let it be known that he wished to become a member of the Prussian Academy of Sciences, which had been founded in 1700 by Frederick the Great's grandfather, King Frederick I, with

the renowned philosopher and mathematician Leibniz as its first president. Spallanzani's membership was accepted with the full support of the king, and he was welcomed with a letter saying, "We are all charmed thus to acquire such a distinguished fellow-member."

After the deaths on the battlefield of his closest military friends, the generals Schwerin, Keith and Winterfeldt, the intimates in Frederick's entourage were mostly men of letters and sciences. Personages like Voltaire, with whom his friendship had begun when he was still crown prince; the French physician and scientist La Mettrie, who also became his reader; and finally Maupertuis, the permanent president of the Academy of Sciences in Berlin, were, together with his physicians, Cothenius and Selle, the king's ever-stronger connecting links with the physical and biological universe. It was these interests, some of which he happened to share with Goethe, that occupied Frederick's mind and completely pushed aside any thought he might have given the budding German romanticism of his period. He also remained totally indifferent to any aspect of German nationalism. And yet Frederick the Great became the hero of the very movements he had disregarded, and the personality and image of the great Prussian king became the idol of all Germany. He himself would have viewed it with strenuous reservations, to put it mildly, had he seen his likeness, as it was frequently shown during the Nazi regime, side-by-side with that of Hitler, who, in the final analysis, destroyed everything Frederick the Great had wanted to build.

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HIP DISLOCATION IN INFANTS

"If a pediatrician sends me an infant—one or two days old, a week old, or three weeks old—with the suggestion that he may have a dislocated hip and I find no evidence of that, I insist on following the child. I put him on double diapers and have him brought back every two or three weeks and examine him for a while until I'm sure, because you can't be certain and you can't categorically say that the child's hip is okay on the basis of one examination."

—THEODORE A. LYNN, M.D., Los Angeles
Extracted from *Audio-Digest Pediatrics*, Vol. 15, No. 20, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057

Information

Some Aspects of Medical Practice at UCLA

C. G. CRADDOCK, M.D., *Los Angeles*

FOR THE PAST EIGHTEEN MONTHS I have been in charge of the Department of Medicine, Outpatient Clinics, at University of California, Los Angeles. The role of a university hospital in health care has always been somewhat ambiguous since the primary obligation of physician training must be integrated with patient care. There has been increasing confusion recently because of shifting socioeconomic factors concerned with health and education, confusion which is evident within this institution as well as within the larger medical community. I am writing to try to clarify some points for physicians who may direct patients to UCLA and do not understand certain facts about the facility.

Financial Base of the Hospital And Clinics at UCLA

UCLA as a *medical school* receives support from the state for a portion of professorial salaries, certain ancillary non-medical personnel, and certain equipment and space. *UCLA Hospital and Clinics* are, of course, an integral part of the medical school's educational functions but the *Hospital and Clinics*, much like any community hospital, must operate on a non-funded fiscal basis. All cost of patient care must be recovered from charges to patients. The latter must be paid by the patient

or by his insurance, private or otherwise. A small proportion of these charges, not recoverable from patients or third parties, can be paid from the hospital's limited clinical teaching fund. This teaching support is so limited that not all patients without resources or insurance can be accepted for medical care at UCLA. The recent shifts in Medi-Cal coverage have exacerbated this difficulty.

The staff at the UCLA Hospital does its best to provide definitive care for persons whom the institution can help with a defined problem, regardless of financial factors. No emergency problem will be turned away. However, the facility cannot accept many patients with non-urgent problems. We have tried to recommend alternative sources for medical care for such persons, but, in truth, there may be no alternative other than further referral to the Los Angeles County Hospital system in many instances. We recognize, of course, that this simply adds to the burden of the county hospitals. However, at present there seems no way to avoid this difficulty.

Hospital and Clinic Fees for Patients in the Department of Medicine Outpatient Area

Patients are classified as private or departmental private patients at UCLA. Both categories of patients are utilized in the teaching and training function of the institution. Private patients are usually referred directly to a member of the full-time or part-time faculty and are handled in a manner similar to that in private hospitals and clinics. The specific faculty member personally supervises the house staff or student management of the problem when the patient is in hospital. Ambulatory patients referred in this way are seen either in the faculty member's office or the Outpatient Department, and are managed by the faculty member. Professional fees are levied in the usual manner and, in the case of full-time faculty, can be used to supplement faculty salaries in a manner and to a limit defined by University policies after all overhead costs of the Hospital and Clinics are met.

Ambulatory patients who come to the Department of Medicine Clinics (not including the emergency room), without referral to a specific physician are classified as departmental private patients. Any professional fees collected from such outpatients for services rendered by physicians

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are used for educational purposes. At present, there is no professional fee for departmental private patients seen as outpatients in the Department of Medicine Clinics (this is not necessarily the case in certain other clinic areas). A clinic fee is charged to defray the cost of maintaining the facility, including the nursing and clerical staffs. Patients admitted to the Department of Medicine in-patient service through the Clinics or Emergency Service may enter as either private or departmental private patients, depending upon many circumstances.

The Pattern of Handling Departmental Outpatients

Departmental patients seen in the Department of Medicine, Outpatient Clinics, generally are handled as follows:

For walk-in, non-emergency patients, the triage desk determines that the problem falls in the general area of Medicine. The patient is then seen in the "Primary Clinic." If the patient telephones, he is given an appointment in the Primary Clinic. The patient's financial resources and insurance are reviewed. The patient is seen by a house officer (first or second year resident or intern supervised by a resident or staff member) who reviews the case, takes an appropriate history and does a physical examination and any laboratory work essential to a determination of the general nature of the problem. If the problem is one requiring more attention, the patient will be evaluated more thoroughly in the General Medical Clinic or the appropriate subspecialty clinic if 50 percent or more of the clinic fees are retrievable. Otherwise, fiscal limitations require that the patient be directed elsewhere unless the problem is one that urgently requires medical attention. Clearly, no one needing emergency care will be turned away. Most patients, however, are self-referred and without urgent or critical medical problems. An occasional outpatient who comes to UCLA is referred by a physician for a subspecialty opinion or procedure and expects the patient to return to him. It is in this area that we feel our greatest responsibility to respond expeditiously and courteously to our colleagues in the medical profession.

We are currently seeking to improve communications and efficiency as rapidly as possible. In the past, for a variety of reasons, there have been some inexcusable lapses, and we are taking

steps to correct this serious deficiency. The referred patient is one for whom we feel that UCLA can render a valid service—for the medical profession and for the teaching function of the institution. UCLA does have the capacity to provide helpful, highly refined subspecialty opinion in many situations. Other patients are sent here by practicing physicians because of extraordinary therapeutic or diagnostic or financial problems. Within the limits of our financial abilities and the time requirements of teaching medicine, we endeavor to care for as many of these patients as we can.

During this period of reexamination, I should like to assure my colleagues in the medical community that if they contact me by telephone or letter concerning their patients with problems in internal medicine I will personally do all I can to expedite their proper management in the Department of Medicine clinics, see that the findings are relayed and that the patient is returned to the referring physician with a full report of findings and opinions.

It may be difficult for a man in practice to see why this type of service has not invariably been available in the UCLA Clinics, as it is at certain other teaching centers such as Mayo Clinic. The reasons lie in the evolution of this medical school from the time when the scope of its facilities was much more restricted, and the means of funding the medical school were quite different from today's.

The UCLA School of Medicine, like most in the country, is under extreme pressure financially and otherwise. Pressures exist also in the UCLA Hospital and Clinics. The solution to these problems will, in a large part, depend upon the ability of the institution as a whole to serve the medical community at large, and this will require better understanding on all sides. I am certain that an institution such as UCLA must find ways to help with medical care in the community in order to remain an educational community asset. The understanding and cooperation of the practicing physician is essential to sustain the quality of medical education and service by this and other medical schools. In turn, the medical school and the UCLA Hospital must prove that it can do its part in a way that is helpful to patients and to practicing physicians while, at the same time, provide the proper environment for education and research.

Congenital Heart Disease In Children

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MARY JANE JESSE, M.D.

*Material Supplied by the
American Heart Association*

THE PHYSICIAN RENDERING primary care has a significant role to play in the management of children with congenital heart disease. He decides when a child should be referred to a pediatric cardiologist or center for definitive diagnostic tests and reviews their recommendations with the parents in order to implement an optimal therapeutic regimen. This necessitates a background of basic physiology and the diagnostic features of the common congenital cardiac lesions, as well as current knowledge of the natural history and results of surgical intervention. His role should be active rather than passive.

The most common lesions seen in older children include ventricular and atrial septal defects (VSD, ASD), patent ductus arteriosus (PDA), pulmonary stenosis with intact septum, tetralogy of Fallot, coarctation of the aorta and aortic stenosis. More complicated lesions are rare, and management has usually begun in infancy.

It is convenient to categorize patients into severity groups dependent upon the natural history and results of operation—for example, mild (excellent prognosis, operation not required), moderate (expert opinions differ, operation dependent upon evaluation of patient's general status), severe (operation definitely indicated), inoperable (surgical mortality unacceptable).

Some lesions result in an increased volume of blood presented to the ventricle resulting in "volume work" (VSD, ASD, PDA) while in others, the ventricle must perform increased "pressure" work to overcome resistance (pulmonic or aortic stenosis, coarctation of aorta, left-to-right shunts complicated by pulmonary vascular obstructive disease).

TABLE 1.—*Ventricular Septal Defects Severity Classification*

	Q_p/Q_s	P_p/P_s
Mild	<1.5	<0.5
Moderate	1.4 to 2.2	<0.5
Severe	>2.2	>0.5
Inoperable	<1.5	1.0

Q_p =Pulmonary Blood Flow. Q_s =Systemic Blood Flow. P_p =Pulmonary Artery Pressure. P_s =Systemic Blood Pressure.

Ventricular Septal Defect

Typical findings in VSD include a thrill in the fourth left interspace and a loud, rough, holosystolic murmur in that area. The natural history of this defect varies with the severity of the hemodynamic abnormality. The clinical course is dependent on the magnitude of pulmonary blood flow and reactivity of the pulmonary vascular bed. The severity of the defects are classified in Table 1.

Indications for early cardiac catheterization are exercise intolerance, cardiac enlargement, congestive heart failure, or evidence of right ventricular enlargement. If none of these problems is present, diagnostic studies are done electively after five years of age. Operation is curative unless the defect is incompletely closed, or heart block is induced.

Atrial Septal Defect

Classical findings in atrial septal defect are a parasternal impact, an ejection systolic murmur at the second left interspace, a widely split fixed S_2 , and electrocardiogram evidence of right ventricular enlargement or rR' pattern in the right precordial leads with roentgen evidence of cardiomegaly and increased pulmonary vascular markings. Operation is indicated unless the defect is very small and the ratio of pulmonic to systemic blood flow is less than 1.5, or severe pulmonary vascular obstruction has resulted in a right-to-left shunt with cyanosis. Surgical mortality in operable patients is less than one percent, and the result is curative.

Patent Ductus Arteriosus

Patent ductus arteriosus is characterized by a crescendo systolic-decrescendo diastolic machinery murmur. Cardiac catheterization is indicated only if the murmur is atypical, or there is evi-

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dence of right ventricular enlargement (RVE). Operation is indicated in symptomatic children and, electively, in all patients at about four years of age. Operative mortality is less than one percent. Correction is contraindicated if there is cyanosis due to a right-to-left shunt.

Pulmonic Stenosis

The findings in pulmonic stenosis include a thrill and a rough ejection systolic murmur in the second left interspace. The lesion is characterized as mild if the peak systolic gradient from right ventricle to pulmonary artery is less than 50 mm of mercury, and severe if the peak systolic gradient is greater than 80 mm Hg. Gradients from 50 to 80 mm of mercury are classified as being moderate. Cardiac catheterization is performed electively after five years of age and earlier if there is clinically detectable cyanosis, cardiac enlargement or ECG evidence of increasing RVE. If RV "strain" pattern is present, diagnostic study is mandatory as an emergency procedure. Operative mortality is less than one percent, and surgical correction relieves the obstruction.

Aortic Stenosis

Congenital aortic stenosis results in a thrill and ejection systolic murmur in the second right intercostal space. The obstruction may be valvar, subvalvar or supravalvar. Severe obstruction may cause angina, syncope, electrocardiographic evidence of left ventricular strain, and even sudden death. Unfortunately, severe pressure loads on the left ventricle may occur without evidence of symptoms, abnormal ECG or chest film. Indications for diagnostic study are urgent if the clinical diagnosis is clear, and angina, syncope, cardiomegaly or a left ventricular "strain" pattern are present. In the asymptomatic child with a typical murmur and thrill, elective catheterization is indicated after five years of age.

Severity is judged as mild when the peak systolic gradient from left ventricle to aorta is less than 65 mm of mercury, severe when the peak systolic gradient is greater than 80 mm or LV "strain" pattern is present. A moderate category includes those with gradients between 65 and 80 mm of mercury and without an ECG "strain" pattern.

The operation is essentially palliative. Resid-

ual aortic stenosis is not uncommon, and late calcific aortic stenosis is common. Aortic insufficiency is not a rare complication, but if mild may be tolerated well through childhood and adolescence. Ultimate valve replacement may be necessary.

Coarctation of the Aorta

Coarctation of the aorta is diagnosed on clinical grounds, by the presence of a differential in blood pressure between the upper and lower extremities. Cardiac catheterization is not indicated unless there is a complicating lesion. Indication for early operation is the presence of severe hypertension, or ECG evidence of left ventricular enlargement. Otherwise, correction should be performed electively between six and twelve years of age. The result is curative.

Tetralogy of Fallot

Tetralogy of Fallot is characterized by a large ventricular septal defect and varying degrees of right ventricular outflow obstruction resulting in RV pressures at or near systemic levels and cyanosis due to right-to-left shunting through the septal defect. The outstanding symptom is decreased exercise tolerance. Sudden decreases in arterial oxygen saturation result in hypoxic spells (increased cyanosis, irritability, and air hunger) and may be lethal. Cardiac catheterization to delineate the anatomy is indicated in all patients in whom operation is contemplated. Two types of surgical approach are available: palliative shunting procedures, or intracardiac repair with closure of the septal defect and relief of outflow tract obstruction.

If the patient is severely symptomatic before the age of five years, a shunting procedure is indicated. Intracardiac repair is indicated in the severely symptomatic child over five years of age, and electively after eight years of age. Palliative shunting procedures in children over five years of age have a low mortality rate and those with good results usually remain satisfactory for five to ten years. Intracardiac repair has been associated with a diminishing mortality rate that is now 7 to 10 percent in many large centers. The long-term results are most promising. Five and ten-year follow-ups have been excellent in those in whom adequate repair has been achieved.

PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H., Director, State Department of Public Health

Noise, the Fourth Pollution

MODERN MAN DEGRADES his environment with polluted water, dirty air, solid waste and, increasingly, noise. Noise, defined as "unwanted sound," intrudes everywhere — in urban, suburban and wilderness areas, in offices, factories, and homes. Both occupational and community noise represent health hazards, such as loss of hearing, interference with sleep and efficiency, and fatigue, and therefore present a challenge to the medical profession.

Because noise is rapidly becoming intolerable, the California Legislature last year requested the State Department of Public Health to appoint an advisory committee of representatives of concerned public and private groups and to report findings and recommendations on specific problems of noise.

The resulting report (A Report to the Legislature on the Subject of Noise Pursuant to Assembly Concurrent Resolution #165, 1970 by the California State Department of Public Health) points out that the most obvious harmful effect of noise is permanent loss of hearing. Although this has been known to occur after a single exposure to a very loud noise, the risk from prolonged exposure, as in the case of industrial or occupational noise, is much greater. Current criteria for preventing hearing loss in industry protect hearing for frequencies ranging from 500 to 2000 cycles per second (cps), the range necessary for understanding speech. But humans can hear sounds

from 20 to 20,000 cps and some enjoyable sounds, such as music in certain ranges, are in the frequencies above 2000 cps. The Department recommends that the reference level of occupational noise be set at 75 decibels (on the A scale) by 1980 since 75 to 85 decibels represent the levels at which hearing loss may occur.

Noise causes physiological stress such as widespread activation of the autonomic nervous system with changes in heart rate, respiration rate, gastric activity, pupil size and sweat gland activity. Studies have been made to evaluate the significance of these effects at the noise levels at which they occur. Present data indicate that the threshold of response is about 65 decibels and becomes pronounced at 80 to 85 decibels.

Noises both inside and outside the home interfere with communication. Sixty decibels is the level of ordinary conversation and is relatively quiet. Normal conversation cannot be carried on if sounds rise above 75 decibels, as is the case with such household appliances as food blenders, garbage disposals and clothes washers. In multi-family dwellings, plumbing systems, elevators, and heating and cooling systems create noises which are transmitted throughout the buildings. The report proposes that noise transmission standards for buildings be established and that building code provisions be instituted to enforce them.

Although people who live near airports are most bothered by aircraft noise, surface transportation noise from trucks, passenger cars, buses and motorcycles offend the most people. Minibikes, snowmobiles, power-boats and other mechanically powered vehicles contribute to transportation noises, as do noises associated with amusement and recreation.

The Department proposes that by 1978 new passenger cars, now permitted to emit 85 deci-

bels, should not emit more than 75, and vehicles 6000 pounds or over, which now may emit 88 decibels, not more than 80. These are substantial decreases, since a reduction of only three decibels represents a 50 percent reduction in noise. Trucks and buses already in operation can be made quieter by using better mufflers and quiet-running tires.

Since transportation is one of the outstanding sources of noise, local ordinances applicable to other sources will not solve the problem unless they also apply to transportation noise. The state and federal governments have set criteria limiting noise for most methods of transportation. The Department recommends that local ordinances include equivalent criteria and that local authorities share in enforcement.

Because freeways are inherently noisy and will be for the foreseeable future, the report points out, they should be separated from residential areas by barriers or freeway designs providing protection from noise. Rural land near freeways should be reserved for uses compatible with the environment, which would exclude schools and residential areas. Similarly, compatible land use zoning should be required in the vicinity of all new airports and existing airports not now surrounded by land devoted to incompatible use.

People vary in their tolerance of noise but to some extent reactions to it are determined by expectations. For instance, people in industrial or commercial areas will generally tolerate more noise than those in urban residential areas. Suburban residents demand more quiet than urban dwellers and rural residents demand the most quiet. Moreover, loudness is not the sole criterion of the distress noise causes. Some noises are incompatible with the environment in which they occur. A snowmobile producing 90 decibels of sound in the wilderness may be much more intrusive than a jet takeoff at the airport producing

110 decibels. And noise criteria are subjective, so that the sound of a motorcycle which is music to the teenager is often a source of anguish to his parents.

Although efforts at noise control have thus far been sporadic, it is possible to establish an effective program. It should include both short-range and long-range goals and should be framed in broad terms rather than only in terms of quieting individual noise sources and building sound barriers. In some urban areas, there may be no way to reduce community noise by short-range measures and a longer-range program may be necessary. For example, mass transit, such as the Bay Area Rapid Transit System, has the advantage of producing much less noise than mass transportation by automobiles.

We now have the technological means to control noise to any desired degree. A first step is to forbid sources of excessive noise where possible and to control existing sources where they cannot be economically replaced. Most new products can be made quiet relatively cheaply, if quiet is built into the original design. This is more effective than relying on secondary techniques, but these must also be applied in the meantime. Noise can be reduced by placing acoustical barriers between the source and the receiver and by enclosing the source with sound-absorbent material. Separating the noise source from the receiver is also a good way to attenuate noise, since each time the distance is doubled, sound is reduced four to six decibels—a substantial decrease.

Excessive noise need not be tolerated as an inevitable component of modern life. People can demand as much quiet as they wish but must then be willing to cooperate in achieving it, part of that cooperation being the added expense which is the cost of quiet. In such efforts at noise abatement, the medical and allied professions can play an important role.

101st

Annual Session

California Medical Association

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San Francisco

Program planners are hard at work formulating presentations of interest and value. For instance,

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Pelvic Cancer in Women

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In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

AKER, CECIL G., South San Francisco. Died July 10, 1971 in Carmel of heart disease, aged 58. Graduate of Washington University School of Medicine, St. Louis, 1938. Licensed in California in 1948. Doctor Aker was a member of the San Mateo County Medical Society.

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BERG, ROBERT W., Selma. Died July 4, 1971, aged 55. Graduate of Western Reserve University School of Medicine, Cleveland, 1943. Licensed in California in 1947. Doctor Berg was a member of the Fresno County Medical Society.

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BURGE, MARTIN HARLESS, San Marino. Died July 21, 1971 in San Gabriel of cerebral vascular insufficiency, aged 76. Graduate of State University of Iowa College of Medicine, Iowa City, 1918. Licensed in California in 1922. Doctor Burge was a member of the Los Angeles County Medical Association.

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CHRISTIERSON, SIGURD VON, San Francisco. Died June 29, 1971 in San Francisco, aged 76. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1922. Licensed in California in 1922. Doctor von Christierson was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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FAIRCHILD, GORDON E., Glendora. Died June 16, 1971 in West Covina, aged 49. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1959. M.D. degree from California College of Medicine, 1962. Doctor Fairchild was a member of the Forty First Medical Society.

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HIRSCHFELD, MERVYN H., San Francisco. Died July 5, 1971 in San Carlos, aged 79. Graduate of University of California Medical School, Berkeley-San Francisco, 1917.

Licensed in California in 1917. Doctor Hirschfeld was a member of the San Francisco Medical Society.

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KULCHAR, GEORGE V., San Francisco. Died July 11, 1971 in Burlingame, aged 69. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1930. Licensed in California in 1930. Doctor Kulchar was a member of the San Francisco Medical Society.

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PETERSON, CARL ANDREW, Palo Alto. Died July 8, 1971, aged 54. Graduate of University of Minnesota Medical School, Minneapolis, 1942. Licensed in California in 1950. Doctor Peterson was a member of the Santa Clara County Medical Society.

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RUTH, EDWARD SAMUEL, Los Angeles. Died July 8, 1971 in Los Angeles of cerebral thrombosis, aged 87. Graduate of The University of Kansas School of Medicine, Lawrence-Kansas City, 1910. Licensed in California in 1919. Doctor Ruth was a member of the Los Angeles County Medical Association.

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RYAN, ALBERT FREEMAN, Los Angeles. Died December 4, 1970 in Los Angeles of thrombosis of cerebellum artery, aged 84. Graduate of Northwestern University Medical School, Chicago, 1913. Licensed in California in 1921. Doctor Ryan was a member of the Los Angeles County Medical Association.

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SALVATER, MAX L., Sacramento. Died July 12, 1971 in Sacramento of myocardial infarction, aged 60. Graduate of Marquette University School of Medicine, Milwaukee, 1939. Licensed in California in 1939. Doctor Salvater was a member of the Sacramento County Medical Society.

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VON DESSONNECK, EMIL S., Daly City. Died July 8, 1971 of heart disease, aged 60. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1938. Licensed in California in 1938. Doctor von Dessonneck was a member of the San Francisco Medical Society.

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YAW, LOUIS R., Riverside. Died July 7, 1971 in Riverside of multiple myeloma, aged 69. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1943. Licensed in California in 1943. M.D. degree from California College of Medicine, 1962. Doctor Yaw was a member of the Riverside County Medical Association.



Mithramycin for Hypercalcemia of Malignant Disease

THOMAS E. GODFREY, M.D., Loma Linda

■ *Mithramycin (Mithracin®) rapidly controlled the hypercalcemia of malignant disease in every patient. This control was temporary, and intermittent administration of the antibiotic was required.*

Hypercalcemia frequently responds to non-toxic maneuvers such as hydration and moderate doses of corticoids. Until the mechanism of action of Mithramycin in hypercalcemia is better understood, caution should be urged in its prolonged use for this purpose.

THE ASSOCIATION OF HYPERCALCEMIA with malignant disease is well established.¹ Four possible mechanisms of this phenomenon have been described: (1) the direct lysis of bone by metastasis, (2) secretion by the tumor of parathyroid peptides, (3) secretion by the tumor of osteolytic sterol, and (4) adrenal insufficiency secondary to metastasis.²

Mithramycin (Mithracin®) is a yellow crystalline compound produced by the actinomyces *Streptomyces plicatus*. It has an empirical formula of $C_{52}H_{76}O_{24}$. The drug is soluble in water and in lower alcohols, but it is unstable in acid solutions, and has a strong ability to chelate with metal ions. It is a potent antineoplastic agent which has been shown to be useful in the treatment of patients with malignant tumors of the testis where successful treatment by surgery or by radiation or by both is impossible.

From the Department of Medicine, Loma Linda University School of Medicine.

Mithramycin was supplied by the John L. Smith Memorial for Cancer Research, Charles Pfizer and Company, Incorporated, Maywood, New Jersey.

Submitted, revised, February 24, 1971.

Reprint requests to: Department of Medicine, Loma Linda University Hospital, Loma Linda, Ca. 92354 (Dr. T. E. Godfrey).

During 1965, mithramycin was evaluated by the author as treatment for 53 patients with a variety of disseminated neoplasms. Hypocalcemia developed during treatment of 28 of the 48 patients where calcium determinations were obtained. Because of this demonstrated ability to lower the blood calcium, the drug was given as treatment to three patients with hypercalcemia secondary to malignant disease. The hypercalcemia was well controlled in each instance. This was reported at a symposium on Mithramycin, Streptonigrin, and Methyl Ester of Streptonigrin that was held at the National Institutes of Health, Bethesda in September 1965.³ Since that time, other reports have appeared in the literature.^{4,5,6,7}

This article summarizes the treatment results of these first three cases and an additional 18 patients subsequently treated.

Material and Methods

Twenty-one patients with symptomatic hypercalcemia secondary to advanced neoplasms were treated with mithramycin. The age, sex, diagnosis, and pretreatment serum calcium concen-

TABLE 1.—Data on 21 Patients Treated with Mithramycin for Control of Hypercalcemia of Malignant Disease

Case	Age	Sex	Diagnosis	Serum Calcium* mg/100 ml		Duration Therapy Days	Total Drug Received mg
				1st Day	6th Day		
1	46	F	Breast Carcinoma	20.0	8.0†	5	3.4
2	56	F	Breast Carcinoma	17.4	9.1	15	10.5
3	48	F	Breast Carcinoma	17.3	8.4	139	58.0
4	30	F	Breast Carcinoma	11.2	10.1	20	4.4
5	55	F	Breast Carcinoma	12.5	9.7	28	4.5
6	56	F	Breast Carcinoma	16.7	10.9	12	4.5
7	51	F	Breast Carcinoma	12.7	9.2	55	13.5
8	61	F	Breast Carcinoma	18.2	11.7††	4	6.0
9	68	F	Breast Carcinoma	18.2	8.2	7	5.0
10	62	F	Multiple Myeloma	16.8	10.1	36	4.5
11	59	F	Multiple Myeloma	14.0	10.2†††	3	3.0
12	46	M	Multiple Myeloma	11.8	7.8	66	4.6
13	52	M	Multiple Myeloma	14.2	8.0	26	5.5
14	65	M	Multiple Myeloma	12.2	10.0	16	1.5
15	53	M	Hypernephroma	12.0	9.4	37	6.0
16	44	M	Hypernephroma	15.0	10.9††††	36	11.5
17	72	M	Carcinoma Lung (large cell anaplastic)	11.6	8.7	19	3.0
18	51	F	Squamous Cell Carcinoma of Soft Palate	21.0	8.0	10	4.5
19	16	F	Adenocarcinoma Pancreas	15.9	12.8	35	9.5
20	85	M	Carcinoma Prostate	14.0	10.7	34	19.5
21	29	F	Reticulum Cell Sarcoma	18.4	9.7	15	4.5

* Normal range 9.0-11.0 mg% Oxford Laboratory modification of the Bett and Frazer method of calcium determination as described in Biochem J 68-13P, 20P, 1958

† 5th day. Expired same day.

†† 4th day. Expired 6th day.

††† 4th day. Expired 5th day.

†††† 5th day.

trations are shown in Table 1. The presenting symptoms of hypercalcemia were principally central nervous system related (lethargy, confusion); although in some cases gastrointestinal symptoms (nausea, vomiting, constipation) predominated. The pretreatment serum calcium concentrations ranged from 11.2 to 21.0 mg per 100 ml with the majority between 14.0 and 16.0 mg.

The daily dosage of mithramycin was usually 1.5 mg but ranged from 1 to 2.5 mg. The drug was added to 1,000 ml of 5 percent glucose in water and given as a 3-hour intravenous infusion. Three successive days of this treatment completed a course of therapy. Intermittent administration of the drug was usually necessary after 10 to 14 days to maintain the serum calcium in the normal range.

Sixteen of the 21 patients had x-ray evidence of bone involvement by malignant disease. Hypercalcemia seemed related to recent androgen

administration in three of the nine patients with breast carcinoma, and to estrogen administration in another three.

Baseline pretreatment tests included serum calcium, phosphorus, alkaline phosphatase, blood urea nitrogen (BUN) and serum proteins. The serum calcium was checked at 12-hour intervals until it returned to normal, then was determined every 1 to 2 days. The other blood tests were checked less frequently. Urinary excretion of calcium and phosphorus was determined before and during treatment in some patients.

Results

Hypercalcemia was successfully controlled in all patients. However, three died of tumor-related causes during the first week of treatment. Subjective improvement usually occurred within 12 hours and a detectable drop in the serum cal-

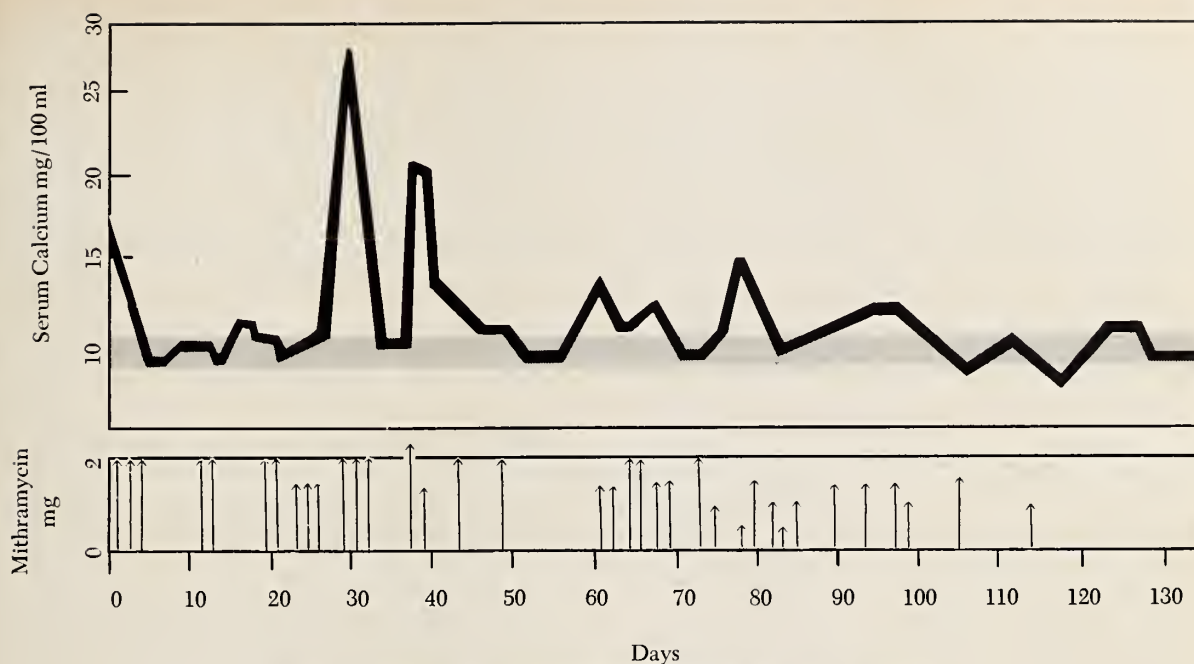


Chart 1.—Details of treatment and response in Case 3, Table 1.

cium concentration was seen at 36 hours. The calcium returned to normal range within 6 days after the start of treatment in all but one patient (Case 16, Table 1). In that instance, the calcium concentration dropped from 15.9 to 12.5 mg per 100 ml within 4 days but then rose to 13.4 mg per 100 ml on the eighth day. An additional 2.0 mg of the drug was necessary on the ninth day to bring the serum calcium into the normal range 12 days after treatment was started.

The serum calcium frequently returned to hypercalcemic levels 10 to 14 days after a course of therapy. This necessitated intermittent infusions of the drug. One patient (Case 3) required mithramycin for 139 days (Table 1).

No resistance to the hypocalcemic effects of the drug was observed. Hemorrhagic problems and hematologic toxicity did not occur, as relatively small amounts of the drug were required for control of hypercalcemia. A cumulative effect of the agent was suggested in patients receiving the drug over long time periods, lesser amounts being required during the second half of the treatment period in this group (Chart 1).

Changes in the serum phosphate paralleled changes in the serum calcium in all but four patients with renal insufficiency. When patients with known hepatic metastasis were excluded, there appeared to be a consistent drop in the serum alkaline phosphatase concentration during

the time the serum calcium values were diminishing. A pronounced drop in the urinary excretion of calcium occurred during treatment while the urinary excretion of phosphorus remained normal.

The BUN was followed in 15 patients. In seven it declined or remained unchanged while in eight there was an increase during treatment. In one patient with myeloma (Case 14) the BUN rose from 66 to 140 mg per 100 ml. In another patient with hypernephroma (Case 16) the BUN increased from 25 to 96 mg per 100 ml. A third patient with breast carcinoma (Case 3) had BUN in the normal range before treatment; three months later, after receiving 58 mg of mithramycin, she died of acute renal failure.

Nausea and vomiting were frequent side effects. It was felt the severity of these side effects could be reduced by administering the drug as a 3-hour intravenous infusion rather than as a rapid intravenous injection. When vomiting occurred, it began about the time the infusion was completed and continued for 6 to 8 hours. The severity was less than that seen following nitrogen mustard administration. Prochlorperazine (Compazine®) was helpful in reducing these side effects.

Discussion

Hypercalcemia often responds to nontoxic maneuvers such as hydration, moderate doses of

corticoids and sodium sulfate infusions. These measures should be used before resorting to newer and possibly toxic drugs such as mithramycin. While mithramycin rapidly and effectively controlled hypercalcemia in every patient in the present series, questions should be raised regarding its renal toxicity. It seems possible that one patient (Case 3) may have died from drug-induced renal necrosis.

The fecal excretion of calcium was not determined during treatment in these cases nor has it been reported by others. This needs to be studied.

Hormone therapy was stopped in six patients with metastatic breast carcinoma when hypercalcemia was discovered. While this maneuver could be expected to control hypercalcemia in hormone-induced states, the precipitate drop in calcium concentrations following mithramycin suggests this drug was responsible for the early control of hypercalcemia in this group.

The hypocalcemic effects of mithramycin were unrelated to control of the tumor. In several patients, tumor progression occurred during a pe-

riod when hypercalcemia was successfully controlled with the drug. No patient experienced symptomatic hypocalcemia as a result of the rapid drop in the serum calcium.

Hypercalcemia should be regarded as a serious complication of malignant disease. The median survival time in these patients was 41 days from the time of diagnosis even though the hypercalcemia was successfully controlled with mithramycin.

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"CHEMICAL CURETTAGE" FOR EXCESSIVE BLEEDING

A woman comes to you complaining of excessive flow or a prolonged bleeding episode. What hormones could you use to stop this flow?

"Pure progesterone, not progesterone combined with estrogen, is one possibility. If you give 25 to 50 mg a day for two or three days, the bleeding will stop or at least decrease. Then following the withdrawal of the progesterone, the women will get a very good sloughing of the endometrium. This is a so-called 'chemical curettage.' This bleeding will last for about three or four days and then stop.

"You have to be sure that the patient understands it will be about eight days before there's a complete cessation of menstruation. Women usually think the bleeding will stop the minute you give the first injection. Then when they bleed rather heavily on the fourth to the eighth days, you'll get a phone call unless you have given the proper explanation beforehand. This is a good way of desquamating the endometrial cavity when you have an unopposed estrogen cause of bleeding, particularly a hyperplastic type of endometrium."

—WILLIAM C. KEETTEL, M.D., Iowa City
Extracted from *Audio-Digest Internal Medicine*, Vol. 16, No. 23, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057

Thyroid Storm

A Review of Cases at University of California, San Francisco

MICHAEL ROIZEN, M.D., *Boston*, AND CHARLES E. BECKER, M.D., *San Francisco*

■ *Retrospective study of the diagnosis and management of the 8 cases of thyroid storm in a series of 400 hyperthyroid patients led to conclusion that thyroid storm is a clinical diagnosis based on a life-endangering illness in a hyperthyroid patient whose hyperthyroidism has been severely exacerbated by a serious precipitating illness, and that storm is manifest by the symptoms of hyperpyrexia, tachycardia and striking alterations in consciousness. No laboratory tests were diagnostic of storm, and the underlying precipitating cause of thyroid storm was the major determinant of survival. Vigorous therapy must include blocking synthesis of thyroid hormones with antithyroid drugs, blocking release of preformed hormone with iodine, meticulous attention to hydration and supportive therapy, as well as correction of precipitating cause of storm. The blocking of the sympathetic nervous system with reserpine or guanethidine or with alpha and beta blocking drugs may be exceedingly hazardous and requires skillful management and constant monitoring in a critically ill patient.*

THYROID STORM IS A LIFE threatening exacerbation of hyperthyroidism. Despite increasing awareness of precipitating factors, metabolic aberrations and treatment, the recent literature still reveals a 20¹ and 60² percent mortality.

During the last five years at the medical center at the University of California, San Francisco, eight patients were treated for thyroid storm. When their hospital records were studied, special emphasis was placed on those events which changed thyrotoxicosis into thyroid storm. It became evident that survival was vitally dependent on the antithyroid therapy and also on rec-

ognizing and treating the precipitating causes of the storm. Two of the three patients who died during thyroid storm were in "good thyroid control" at the time. The reason for death was that their precipitating illnesses were neither completely recognized nor adequately treated.

Clinical Material and Methods

The University of California medical center in San Francisco, a 500-bed referral center for the San Francisco Bay Area and Northern California, had approximately 60,000 hospital admissions during the survey period. The 400 hospital records coded for hyperthyroidism between July 1965 and June 1970 were analyzed for thyroid storm. All patients in the survey were either followed by their private physicians or in the Uni-

At the time of writing this report Mr. Roizen was a fourth year medical student, University of California, San Francisco; Dr. Becker is from the Department of Medicine, University of California, San Francisco.

Submitted, revised, January 19, 1971.

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versity of California thyroid clinic. A diagnosis of thyroid storm was considered to be established when the house staff and attending physicians used the words "thyroid crisis" or "thyroid storm" in the discharge diagnosis. Nine such episodes of storm occurred in eight patients during the study period. Judged by this review, only one hyperthyroid patient not originally diagnosed as having storm met the criteria for storm, and one patient in whom the condition was diagnosed did not meet our criteria of thyroid storm.

Laboratory studies were performed either in the clinical laboratories or the Nuclear Medicine Department of this hospital, or by referral in Clinical Laboratory Associates in Berkeley, California. Accepted normals for protein bound iodine (PBI) are 5 to 8 mg per 100 ml, butanol extractable iodine (BEI) 3.2 to 6.4 mg per 100 ml, true T4 (by displacement) 3.0 to 7.3 mg per 100 ml, 1½ hour radioiodine uptake less than 15 percent, 5-hour radioiodine uptake 8 to 30 percent, 24-hour radioiodine uptake 15 to 45 percent, T3 uptake 25 to 35 percent, and cholesterol 160 to 260 mg per 100 ml.

Results

Age and Sex. Only 48 (12 percent) of the 400 hyperthyroid patients studied were males. All eight thyroid storm patients were females with an age range from 17 to 60 years and average of 38 years.

Thyroid History. Four of the eight storm patients had a family history of thyroid dysfunction. By either suggestive symptoms or a physician's diagnosis seven of the eight patients had a previous history of hyperthyroidism. The average duration of hyperthyroid symptoms before the onset of thyroid storm was 1.6 years. At the time of admission five of the eight were receiving anti-thyroid medication while two others had recently discontinued antithyroid therapy.

Admitting Diagnosis. The admitting diagnosis of thyrotoxicosis was made in all eight cases, but thyroid storm was the major diagnosis in only five. Subsequently, all eight had storm listed as one of the prominent discharge diagnoses. In six additional patients "impending thyroid storm" was the admitting diagnosis, but in no case did this progress to frank storm and in none of these cases was thyroid storm diagnosed on discharge.

Precipitating Factors. Infection, drug reactions, and vascular syndromes were the most

TABLE 1.—*The Incidence of Probable Participating Factors in Eight Cases of Thyroid Storm*

<i>Infection</i> , three cases
Aseptic Meningitis, Cellulitis, Pneumonia
<i>Vascular Syndromes</i> , three cases
Pulmonary emboli, Bowel infarction (vasculitis), Renal infarction
<i>Drug Reaction or Drug Therapy</i> , three cases
Mellaril® (thioridazine); Itrumil® (iothiouracil); propranolol
<i>Discontinuance of Antithyroid Therapy</i> , two cases
<i>Surgical Operation</i>
Subtotal thyroidectomy
<i>Radioactive Iodine Therapy</i> , one case

common precipitating events in this series. Each complication contributed to the precipitation in three of the nine cases. Withdrawal of antithyroid therapy contributed to precipitation in two cases, and I¹³¹ therapy probably in another. (Table 1).

Symptoms of Thyrotoxicosis. All eight patients had loss of weight (40 pounds in one month and 30 pounds in three months were the most striking). Only four manifested eye signs of exophthalmos, lid lag or decreased convergence at the height of the storm. All eight had hyperpyrexia ranging from 38.5 to 41°, with a mean of 39.8°C; respiratory rate averaged 29 per minute, ranging from 20 to 40.

CNS Signs and Symptoms. All patients had a fine tremor while three complained of myalgia. Four patients were judged psychotic and three others manifested inappropriate affect accompanied by disorientation. Six patients became frankly comatose. Three patients who were responsive but "apathetic" subsequently died.

Cardiovascular Symptoms. The average of heart rates during storm in eight cases was 156 per minute and the range was from 120 to 200. Four patients had atrial fibrillation and one had paroxysmal atrial tachycardia. The average pulse pressure was 78 mm of mercury and the range was from 40 to 100. The diagnosis of congestive heart failure was made in three patients. (Two patients had been treated with propranolol, which may have exacerbated the congestive heart failure—a possible drug effect which apparently was not recognized clinically). All three patients with heart failure subsequently died.

Gastrointestinal Symptoms. All eight patients had moderately severe diarrhea, while only four vomited and complained of abdominal pain.

Perforation of the bowel developed in two of those with abdominal pain. Because their gastrointestinal symptoms were attributed to thyroid storm at a time when high doses of corticosteroids were being administered, the diagnosis of perforation was delayed.

Liver Function. Early in storm, the three patients who died had abnormalities of liver function characterized by abnormal prothrombin time, reversed albumin-to-globulin ratio and an elevated bilirubin level. It is of note that all three had some degree of congestive heart failure and that none had SGPT, SGOT, or alkaline phosphatase measurements performed. No significant abnormalities of liver function tests occurred in any of the surviving patients.

Renal Function. One dehydrated patient had a depressed creatinine clearance during storm, with reversion to normal by the time of discharge. One of the two patients who died with prerenal azotemia had bilateral renal infarction at postmortem examination.

Thyroid Gland Size and Function Tests. Although results of all thyroid function tests performed during storm were very abnormal, some of the non-storm hyperthyroid patients had test values even more abnormal than the storm patients. The true T₄ level in two patients was 17.3, and 17.8 mg per 100 ml (normal below 7.3 mg). In three patients the BEI levels were 15.4, 20 and 14 mg per 100 ml (normal below 6.4 mg), and in these three, cholesterol levels of 140, 104, 102 and 72 mg per 100 ml were recorded during storm. In every patient, test results were more elevated during storm than either before or after storm. Five patients had diffuse enlargement of the thyroid gland, and in two cases nodular enlargement was noted. Only one patient had no apparent increase in the size of the thyroid gland; pathologic examination in that case revealed hyperactivity without enlargement.

Other systems. There were no consistent hematologic, adrenal or carbohydrate metabolism abnormalities noted.

Discussion

What makes the diagnosis of storm? Thyroid storm is classically defined as a dramatic, life threatening, exacerbation of thyrotoxicosis, manifested by high fever, tachycardia out of

proportion to the fever, and various other abnormalities of cardiovascular, hepatic and central nervous systems.^{1,3,4,5,6,7,8} In the present series the precipitating events of storm and their treatment, not the thyroid abnormalities, apparently determined the survival of the patient. We conclude that thyroid storm is a clinical diagnosis based on a life endangering illness in a hyperthyroid patient whose hyperthyroidism has been severely exacerbated by another serious illness; the symptoms manifested by a storm patient are those of exacerbated hyperthyroidism—tachycardia, fever and striking alterations in consciousness.

What precipitates storm? (Table 1) In this small series, thyroid storm evolved from hyperthyroidism when increased metabolic demands were introduced from extrathyroidal sources, such as infection, pulmonary emboli or drug reactions. Dangerous drug reactions with suspected vasculitis appear to be an unusual but life threatening precipitating cause of storm. Three of our patients had such a reaction, and in one it resulted in bowel infarction. Digitalis intoxication is the only drug reaction documented in the literature as a precipitating cause of storm.^{9,10} One hyperthyroid patient presented with headache, which was initially attributed to thyroid storm but subsequently proved to be caused by aseptic meningitis. Another patient had severe cellulitis and another pneumonia. Thus the precipitating events of storm may present serious problems by themselves, and would probably necessitate admission to hospital even if there were no thyroid abnormalities.

Laboratory Findings. Thyroid storm did not appear to be a laboratory diagnosis, and although the thyroid function tests of a storm patient were grossly abnormal, quite a few non-storm hyperthyroid patients had values exceeding those of the storm patients. A poor prognosis in our series of nine cases of storm was associated with severe central nervous system dysfunction, congestive heart failure, and severe abdominal pain. The results of laboratory tests of thyroid function in the nine storm patients improved with therapy.

Therapy of Thyroid Storm. Therapy for this acute medical emergency is aimed at decreasing the production of thyroid hormone, decreasing the release of thyroid hormone, blocking the peripheral action of the thyroid hormones, and care-

fully treating the precipitating cause while making special effort to support vital function.

Iodine may be given orally or intravenously to a critically ill patient, as 1 to 2 grams of sodium iodide, to prevent release of the preformed hormone. This is the most critical proven form of therapy for storm, since it acts immediately to block release of the preformed hormones.

Large doses of antithyroid drugs are usually given to decrease synthesis of thyroid hormones. Large doses of propylthiouracil (1 gram in 24 hours in divided doses every two to four hours given orally or by nasogastric tube) will generally provide adequate therapy. Parenteral therapy is not readily available but can be done by special pharmacy procedures in an extreme emergency. The blockade of thyroid hormone synthesis by the antithyroid drugs is essential since iodine therapy will provide substrate for further hormonal synthesis. These antithyroid drugs will require several days for their effects to be noted. Hence iodine is required for its immediate effect.

Reserpine,^{8,11,12} guanethidine^{1,13,14} and more recently alpha¹⁵ and beta^{16,17,18} blocking drugs have been advocated to (apparently) antagonize the peripheral actions of the excess thyroid hormones. The full benefit of this therapy must be evaluated in the light of its possible risks, such as emotional depression, abdominal pain, postural hypotension, worsening of congestive failure, bronchospasm, and rapid release of histamine or catecholamines. The side effects must be judged in relation to the established effectiveness of more conventional therapy for hyperthyroidism and the precipitating events of the storm. Advocates of catecholamine antagonist medications for storm patients base their use on published reports detailing decreased storm mortality; these reports may be influenced by their authors' definition of storm and consequently the inclusion of patients with less severe thyrotoxicosis. The reports^{1,8,11,13,14,15,16} are not controlled and, thus, comparison with previous reports neglects progress in support of vital functions and in treating the precipitating cause of thyroid storm. Other advocates¹⁹ also state reservations as to utilizing sympathetic blockade.

Indiscriminate use of corticosteroids²⁰ is also to be avoided, since it may alter body defense mechanisms and may so change vital signs of the patient that gauging the effectiveness of therapy is made difficult.

The most critical therapy, as judged by experience in the present series, concerns the treatment of the precipitating events and the support of vital functions. Dehydration must be treated, albeit with care to avoid circulatory overload and hyponatremia. Intravenous glucose and vitamins are advised.⁵ Infection must be treated with appropriate antibiotics. Hyperpyrexia should be treated with hypothermic blanket, sponge baths and rectal aspirin, with care taken to avoid rapid changes in temperature and cardiovascular collapse.

In one case in the present series the patient survived what was termed "post thyroidectomy storm" with only supportive therapy. This case would not meet our criteria for storm. Other patients received combined therapy but three patients still died of associated illness or precipitating causes of storm. Two patients died with bilateral renal infarctions. One of these patients had multiple large cerebral infarctions, and the other also had multiple myocardial infarctions, perhaps secondary to drug induced vasculitis.

Comparison with Other Reports

As to the average age of the patients, the high proportion of females, the hyperthyroid symptoms, the laboratory values and the therapy given, the present series did not differ greatly from other reported series.^{1,2,7,9,10,21} However, our small series did differ from others in seriousness of the precipitating factors, in the prevalence of central nervous system symptoms, and in the proportion of cases in which storm developed in hyperthyroid patients. Only one of our patients died with storm not under complete control, while in all other series the reports indicate the storm itself rather than the precipitating events, was the cause of death. Our small series had no males, while other series suggest a larger percentage of males in storm compared with those with uncomplicated hyperthyroidism. Our total of 12 percent male hyperthyroid patients does not differ from that of other series. Only 2 percent of our hyperthyroid patients were in storm and only 1 percent had had previous crises, as contrasted with Waldstein's⁷ 7 percent incidence of storm in hyperthyroid patients. The mortality in this series, although high, draws attention to details of improving therapy relative to previous studies. The danger of accelerating congestive heart fail-

ure with beta blocking drugs, which occurred in two of our critically ill patients who died, illustrates the possible hazards of nonconventional therapy.

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SOME BREAST CANCER RECURRENCE CAN BE EFFECTIVELY TREATED

"Three types of recurrent breast cancer can be effectively treated by local therapy, with long-term survival as a frequent result: the parasternal recurrence coming from internal mammary node metastasis, a solitary recurrence in the flab, and a recurrence in the axilla. All of these can occur by direct lymphatic drainage from the primary tumor without the necessity of having systemic disease. You shouldn't throw up your hands when you get a solitary recurrence. You ought to go after it very aggressively either by x-ray therapy or surgery. These are not the patients on whom you do an adrenalectomy or a hypophysectomy."

—JEROME A. URBAN, M.D., New York City
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Aspirin-Induced Prolongation of the Ivy Bleeding Time

Its Diagnostic Usefulness

MERVYN A. SAHUD, M.D., AND RICHARD J. COHEN, M.D., *San Francisco*

■ *Ivy bleeding time values before and two hours after ingestion of 600 mg of aspirin (aspirin tolerance test) were studied in normal persons, in patients with a disorder of primary hemostasis and in patients with various coagulation factor deficiencies. Aspirin produced a significant prolongation of the bleeding time in patients with von Willebrand's disease, uremia, and primary platelet disease, and in two patients with Factor XI deficiency. Dextropropoxyphene hydrochloride caused no prolongation of the bleeding time in normal persons.*

INGESTION OF ACETYLSALICYLIC acid (aspirin, A.S.A.) prolongs the bleeding time in normal persons.¹⁻⁶ The degree of prolongation varies with the bleeding time technique used (Duke,⁷ Ivy,⁸ or Borchgrevink⁹), the dosage of the drug given,¹⁰ and the time between the ingestion of drug and the performance of the test. The mechanism responsible for prolongation of the bleeding time after aspirin ingestion appears related to the ability of this drug to impair platelet release of adenosine diphosphate.¹¹

The present study was undertaken to define precisely the limits of prolongation of the Ivy bleeding time in normal persons exactly two hours after ingestion of 600 mg aspirin (the as-

pirin tolerance test). The aspirin tolerance test was also performed on patients with von Willebrand's disease, uremia, primary platelet disease, or a congenital coagulation factor deficiency other than Factors VIII or IX. In addition, the effect of dextropropoxyphene hydrochloride on the bleeding time of normal persons was investigated.

Materials and Methods

The bleeding time was measured before and exactly two hours after ingestion of aspirin (acetylsalicylic acid, N.F.), 600 mg, in 44 normal persons with no evidence of a hematologic abnormality, in five patients with von Willebrand's disease, in ten patients with uremia (six of whom were undergoing chronic hemodialysis), in seven patients with well documented primary platelet disease,¹² and in seven patients with Factor V, VII, XI, or XII deficiency. Primary platelet disease refers specifically to a familial bleeding disorder in which the principal char-

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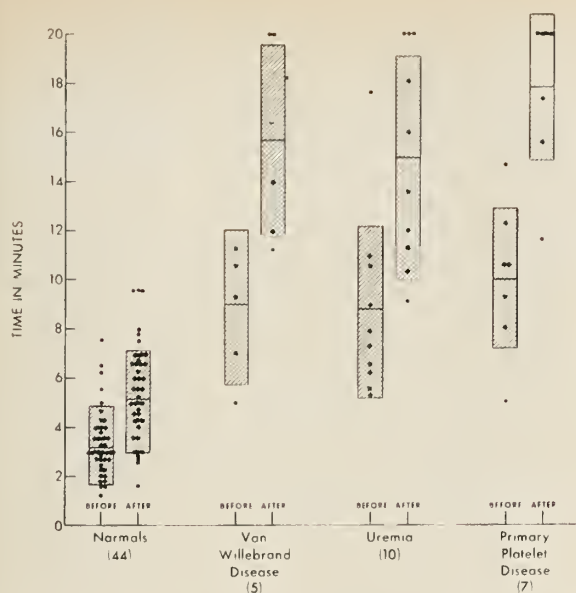


Chart 1.—Ivy bleeding time before and 2 hours after ingestion of 600 mg of aspirin in normal controls and in patients with hemostatic disorders. Each dot represents the mean of three bleeding time incisions. The shaded column represents ± 1 S.D. and the horizontal bar, the mean for that group.

acteristic is defective collagen-induced and epinephrine-induced platelet aggregation but normal clot retraction and factor VIII levels. In 19 of the 44 normal controls, the bleeding time was also measured before and two hours after administration of 65 mg of dextropropoxyphene hydrochloride. Bleeding time was measured by the method of Ivy.¹³ Three incisions, 5 mm deep and 2 mm wide, were made in the volar aspect of the forearm with a spring-loaded lancet,¹⁴ using an ASR Sterisharp No. 11 scalpel blade.* Standardization of the incision may be assured by a 5 mm deep incision with any brand of No. 11 blade since such a technique conveniently produces an incision width of exactly 2 mm without need for further lateral movement. The mean (± 1 S.D.) bleeding time for the three incisions was determined; any single bleeding time greater than 20 minutes was scored as 20 minutes. Measurements were carried out at random by four hematologists. Data were analyzed by Student's *t*-test.

Results

In 44 normal controls, mean bleeding time increased significantly ($P < .001$) from 3.2 ± 1.5

TABLE 1.—Ivy Bleeding Time and Factor VIII Levels Before and After the Aspirin Tolerance Test in Five Patients with Von Willebrand's Disease

Patient	Before Aspirin Ingestion		After Aspirin Ingestion*	
	Mean Bleeding Time (minutes)	Factor VIII Level (%)	Mean Bleeding Time (minutes)	Mean Prolongation of Bleeding Time (minutes)
A	11.3	30	14	2.7
B	5.0	33	11.3	6.3
C	10.7	2	20	9.3
D	7.0	7.4	12	5.0
E	9.3	45	20	10.7

* 600 mg orally.

minutes before aspirin ingestion to 4.9 ± 2.0 minutes after aspirin ingestion (Chart 1); the mean prolongation was 1.7 minutes. In the ten patients with uremia (two of whom had mild thrombocytopenia, 121,000 and 124,000 platelets per cu mm) mean bleeding time also increased significantly ($P < .01$) from 8.8 ± 3.8 to 15.0 ± 4.4 minutes after aspirin ingestion (Chart 1). In the patients with either von Willebrand's disease or primary platelet disease the bleeding times were, respectively, 8.7 ± 3.5 and 10.1 ± 3.3 minutes before aspirin and 15.6 ± 4.6 and 17.7 ± 3.4 minutes after aspirin, and these proved to be highly significant in both groups ($P < .01$). In the five patients with von Willebrand's disease, there was no relationship between the degree of prolongation of the bleeding time and Factor VIII levels (Table 1). The mean bleeding time for all 22 patients with a hemostatic disorder increased significantly ($P < .001$) from 9.8 ± 3.8 minutes before aspirin ingestion to 16.2 ± 3.6 minutes after aspirin; the mean prolongation of the bleeding time was 6.7 minutes. Prolongation of the bleeding time after aspirin in patients with a coagulation factor deficiency is shown in Chart 2. The only significant prolongation of bleeding time—that is, 7 and 8 minutes—occurred in the two patients with Factor XI deficiency. (Factor XI quantitative assay <1 percent and 3 percent respectively.¹⁵) Dextropropoxyphene hydrochloride had no effect on the bleeding time in any of the 19 normal persons tested (3.2 ± 1.2 minutes before and 3.4 ± 1.4 minutes after aspirin). No significant difference was found between the results of two and three bleeding time incisions, regardless of whether the subject was normal or abnormal or whether or not aspirin had been ingested.

*The dimensions of the first 10 mm of any commercially available No. 11 scalpel blade are exactly the same as those of a Bard Parker No. 11 blade.

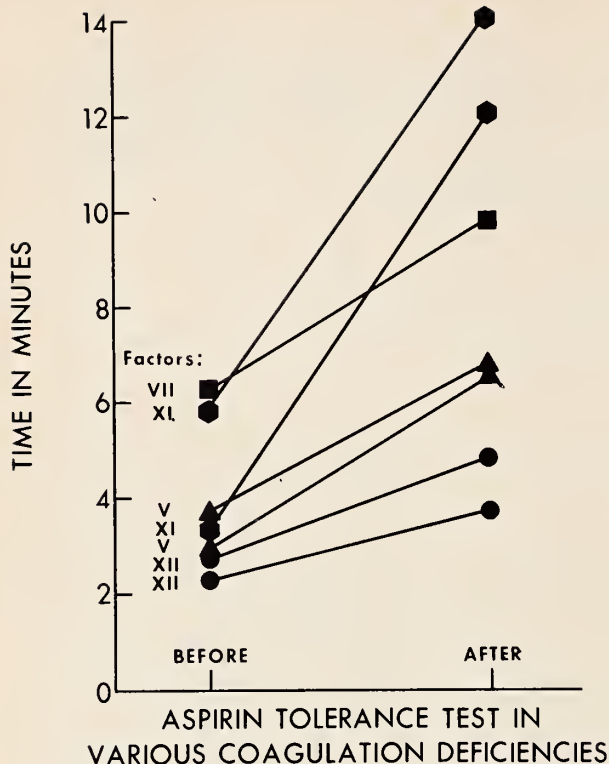


Chart 2.—Ivy bleeding time before and 2 hours after ingestion of 600 mg of aspirin in seven patients with severe congenital coagulation factor deficiencies.

Discussion

The results indicate that the aspirin tolerance test can be standardized for use as a diagnostic procedure for the detection of hemostatic dysfunction. This test caused a mean prolongation of the Ivy bleeding time of 1.7 minutes in normal persons, and only one had a prolongation of greater than 4 minutes (5.3 minutes). These results contrast sharply with the mean bleeding time prolongation of 6.7 minutes produced by the aspirin tolerance test in the 22 patients with disorders of primary hemostasis.

Quick has stressed the value of the aspirin tolerance test in detecting von Willebrand's disease by prolonging the Duke bleeding time of those patients initially presenting with normal or borderline bleeding time.^{3,16} The severe prolongation of the bleeding time he observed using the Duke technique has not been observed consistently by other investigators using the Ivy technique.^{4,17} It is important to recognize that an abnormal result in the aspirin tolerance test is not specific for von Willebrand's disease, as it is

found in a number of disorders of platelet function such as uremia and primary platelet disease. There appears to be no correlation between Factor VIII levels in patients with von Willebrand's disease and their bleeding time response to aspirin (Table 1).

Based on our data using the Ivy method, any person responding to the aspirin tolerance test with a mean prolongation of the bleeding time of 6 minutes or longer should be suspected of having a hemostatic defect. Using this criterion, further studies on all of our suspect patients have confirmed an abnormality in hemostasis. However, we have also noted a post-aspirin prolongation of the bleeding time of less than 6 minutes in patients with confirmed hemostatic abnormalities. Therefore, a normal value for the aspirin tolerance test does not exclude the existence of a bleeding diathesis.

Aspirin was first noted to have an adverse effect on the Duke bleeding time in patients with hemophilia in 1955.¹ In 1967, Quick¹⁶ observed that a profound prolongation of the bleeding time occurred after aspirin ingestion in patients with either hemophilia A or B and suggested that aspirin might enhance the bleeding potential of these patients. Kaneshiro et al¹⁷ also observed prolongation of the Ivy bleeding time after aspirin in some but not all patients with severe hemophilia A or B, and noted a normal response to the aspirin tolerance test in patients with mild hemophilia. Our limited studies of patients with severe congenital deficiency of Factors V, VII, XI or XII seem to indicate that Factor XI deficiency is associated with an abnormal bleeding time response to aspirin. It should be noted that several observers^{18,19,20} have reported an unusual condition in which a long bleeding time has been associated with factor XI deficiency apparently unrelated to aspirin ingestion. However, Kaneshiro et al found no post-aspirin bleeding time abnormality in three patients with Factor XI deficiency. Perhaps these contrasting findings are related to the differences in the bleeding time technique used. Quick²¹ reported that two patients with Factor II deficiency and two with Factor VII deficiency had a bleeding time prolongation after aspirin but the results are difficult to interpret since the length of post-aspirin prolongation for normal subjects was not defined.

It is clear from the pronounced prolongation of bleeding time produced by aspirin in patients

with von Willebrand's disease, uremia or primary platelet disease why this medication is potentially dangerous in any patient with defective hemostasis. One uremic subject in this study bled heavily from the bleeding time incision sites after aspirin ingestion and required blood transfusions before the bleeding problem was controlled. Any patient with an abnormal response to the aspirin tolerance test as defined herein should be observed for subsequent bleeding complications. The lack of effect of dextropropoxyphene hydrochloride on the bleeding time of the normal subjects we studied suggests that this drug is safe for use in patients with hemostatic disorders who require oral analgesics. Acetaminophen has also been shown to have no untoward effect on the Ivy bleeding time in normal subjects.²²

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TOTAL INTRAVENOUS HYPERALIMENTATION TO PREVENT SHOCK

"From the standpoint of the prevention of shock in susceptible, debilitated patients, one of the greatest advances in recent years was the use of total intravenous hyperalimentation described by Dudrick. . . . He showed that nutrients can be administered in amounts exceeding basal requirements by 200 percent. Over 500 patients were treated by this technique and were maintained in positive nitrogen balance. Forty infants so treated maintained normal growth and development. The basic mixture infused is hypertonic and consists of 20 percent glucose, 5 percent protein hydrolysate, vitamins, sodium, potassium, magnesium, and chloride. Adult patients are gradually brought up to 24-hour volumes of 5 liters infused through meticulously cared-for central venous catheters."

—LOUIS R. M. DEL GUERCIO, M.D., New York City
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Disorders of Amino Acid Metabolism—1971

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OVER THE PAST TWENTY YEARS the number of disorders to which we are able to assign a known enzymatic defect in amino acid metabolism has increased strikingly. Even so, they are relatively uncommon, and their importance lies, in part, in the insight they offer into the normal development and function of the human nervous system. In some of the disorders, such as cystathioninuria, hyperprolinemia and hydroxyprolinemia, the association of a neurologic disturbance may be fortuitous and merely the result of subjecting retarded children, a highly selected group, to biochemical examination. A survey of the normal adult population for the incidence of inborn errors of amino acid metabolism is needed to determine which of the conditions mentioned in this review represent harmless metabolic variants.

Phenylketonuria

Phenylketonuria (PKU) is an inborn error of metabolism due to the inability to convert phenylalanine to tyrosine; it produces mental retardation, seizures, and imperfect hair pigmentation. Folling in 1934 first called attention to the condition.¹ Since then the disease has been found in all parts of the world, although it is rare in Negroes or in Jews of European descent. Its frequency in the United States, as determined by screening programs, is approximately 1 in 14,000. It is transmitted as an autosomal recessive disorder.

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The metabolic defect in PKU is a failure in the hydroxylation of phenylalanine to tyrosine. Phenylketonuric children are born with only slightly elevated phenylalanine blood levels, but due to inactivity or absence of phenylalanine hydroxylase, the amino acid derived from food proteins accumulates in serum and cerebrospinal fluid and is excreted in large quantities. In lieu of the normal degradative pathway phenylalanine is converted to phenylpyruvic acid, phenyllactic acid and phenylacetylglutamine. The transamination of phenylalanine to phenylpyruvic acid is sometimes deficient for the first few days of life, and the age when phenylpyruvic acid may be first detected varies from 2 to 34 days. From the first week of life on, o-hydroxyphenylacetic acid is also excreted in large amounts.

Alterations within the brain are non-specific, usually confined to white matter, and probably progress in severity with increasing age. They include an interference with the normal maturation of the central nervous system, defective myelination, and a cystic degeneration of white matter.²

Phenylketonuric infants appear normal at birth. During the first two months of life, vomiting, often projectile, and irritability are frequent. By four to nine months delayed intellectual development becomes apparent.³ In the classic case, mental retardation may be severe, precluding speech and toilet training, and the Intelligence Quotient is under 50. Seizures are common in the more severely retarded. These usually start before 18 months of age and may cease spontaneously. During infancy they may take the form of infantile spasms, and later grand mal attacks.

TABLE 1.—Screening Tests for Metabolic Defects

Condition	Ferric Chloride	DNPH	Nitroprusside
Phenylketonuria	Green	+	—
Maple Syrup Disease	Navy Blue	+	—
Tyrosinosis	Pale Green (transient)	+	—
Histidinemia	Green Brown	±	—
Hyperglycinemia	Purple	+	—
Methylmalonic Aciduria	Purple	+	—
Homocystinuria	----	—	+
Cystinuria	----	—	+
Glutathioninuria	----	—	+

The typical patient is blond and blue eyed, with normal, and often pleasant features. The skin is rough and dry, and there may be eczema. A peculiar musty odor, attributable to phenylacetic acid, may suggest the diagnosis. Significant neurological abnormalities are rare, although microcephaly, and a mild increase in muscle tone, particularly in the lower extremities, may be present. Older children are restless and hyperactive; and are inclined to self-stimulative movements of the body and hands. In institutionalized patients there may be intellectual deterioration, owing perhaps to environment, perhaps to the natural history of the disease.

A variety of electroencephalographic abnormalities has been found, but hypsarrhythmic patterns, recorded even in the absence of seizures, and single and multiple foci of spike and polyspike discharges are the most common.⁴

Untreated PKU is not invariably accompanied by intellectual deficit. There are a number of phenylketonuric persons with intelligence quotients above 90, although having classic biochemical features of the condition. Although the incidence of spontaneous abortions is high, a number of PKU women have had children; most of the offspring, although heterozygous for PKU, showed prenatal and postnatal growth retardation, microcephaly, severe intellectual delay, and in a few instances major congenital malformations. It seems likely that the high amino acid level in the pregnant PKU mother may damage the fetus.⁵

The diagnosis of PKU can be suspected from the clinical features of the disease and from the examination of the patient's urine by the addition of ferric chloride. In inadequately preserved specimens, phenylpyruvic acid decomposes and the ferric chloride test becomes negative. The

addition of a dilute solution of 2,4-dinitrophenylhydrazine produces a copious yellow precipitate in both fresh and old specimens (Table 1). For routine screening on infants a simple stick test (Phenistix®) is available for use on wet diapers. Confirmatory evidence can be obtained by finding an elevation of plasma phenylalanine. These may already be abnormal in the cord blood of PKU infants, and rise rapidly within a few hours of birth. Inasmuch as there may be a delay in the appearance of phenylpyruvic acid, both the ferric chloride and the dinitrophenylhydrazine tests are inadequate for the diagnosis of PKU during the neonatal period. A program for routine screening involving the microbiological or spectrofluorometric estimation of blood phenylalanine levels has been instituted in California.⁶

The widespread use of screening programs to detect the newborn infant whose blood phenylalanine concentration is higher than normal has uncovered several other conditions that are associated with elevated blood phenylalanine levels during the neonatal period.⁷

Aside from phenylketonuria a variant, previously termed "atypical phenylketonuria," is the most common. On a normal protein intake patients with this condition have blood phenylalanine between 7 mg and 20 mg per 100 ml. This contrasts with the classic PKU patient whose phenylalanine levels are 20 mg per 100 ml or higher. The gene distribution of this entity differs from that of phenylketonuria, with a relatively high prevalence amongst Jews of European descent. Less commonly, a defect in phenylalanine hydroxylation is coupled with a temporary or permanent abnormality of phenylalanine transamination. In these patients the excretion of phenylpyruvic and o-hydroxyphenylacetic acids is inappropriately low for the serum phenylalanine concentrations, and the ferric chloride test is negative on a normal diet and may become only slightly positive during a phenylalanine load. In yet another variant the phenylalanine tolerance improves gradually over the first few months of life, but while the ability to metabolize phenylalanine is greater than in PKU, it is never normal.

In addition, elevated blood phenylalanine levels are observed in a large proportion of premature infants, particularly those receiving a high protein formula. In all these patients tyrosine levels are decidedly increased as well.

In view of the existence of these variants of PKU, the diagnosis of PKU can only be made if the following criteria are satisfied:

- Blood phenylalanine 20 mg per 100 ml or greater, with normal blood tyrosine levels.
- In untreated infants a positive ferric chloride test by 2 to 36 days of age.
- When the infant is temporarily returned to a normal diet between four and nine months of age, the blood phenylalanine concentration rises to 20 mg per 100 ml or higher, and he begins to excrete phenylpyruvic acid.
- After an acute phenylalanine load, the blood tyrosine concentration does not rise.

The distinction between PKU and phenylalaninemia is more than academic. Children with phenylalaninemia do not fare well on dietary therapy. Their phenylalanine levels tend to fall precipitously, and they are likely to have side reactions such as hypoglycemia and symptoms of protein deficiency. These have been known to induce intellectual retardation and other neurological symptoms.⁸

The generally accepted therapy for PKU restricts the dietary intake of phenylalanine, using a commercially available casein hydrolysate from which the amino acid has been removed. Generally, patients tolerate this diet well, and within one to two weeks the serum phenylalanine concentration becomes normal. Various complications of dietary treatment, all due to insufficient intake of phenylalanine, include osteoporosis, poor weight gain, and cutaneous lesions. There is also some evidence that prolonged nutritional deprivation during infancy interferes with intellectual development.⁹

Sample menus low in phenylalanine have been given in the literature.¹⁰ Frequent serum phenylalanine determinations are essential to ensure adequate regulation of the diet. As restriction of phenylalanine intake has definite inherent risks, the criteria for initiating treatment of infants needs re-evaluation. Infants whose phenylalanine levels remain below 20 mg per 100 ml do not appear to become retarded, and there is no justification for treating them. At present we have insufficient evidence for or against the need of treating children whose blood phenylalanine level is higher than 20 mg per 100 ml but who do not excrete phenylpyruvic acid. Restriction of the diet is therefore indicated.

On a low phenylalanine diet seizures disap-

pear and the electroencephalogram often reverts to normal. Abnormally blond hair regains its natural color. The effects on mental ability are less clear-cut. In the experience of Fuller and Shuman^{11,12} treated PKU children fell into a tri-modal distribution with respect to their I.Q. The age at which therapy was initiated did not determine into which of the three groups a given child fell. However, infants under 18 months of age whose blood phenylalanine levels were maintained under 5 mg per 100 ml had a decrease in intellectual performance. Patients who were started on treatment before six months of age, some of whom may have had phenylalaninemia, were represented only in the two higher performance modes. Even when the measured I.Q. is normal, neuropsychological handicaps, which result in poorer school progress than would be predicted from the I.Q. alone are common.¹³ Minor structural malformations of the central nervous system may well be responsible for this difference.² In other instances normal intellectual development may be possible in the absence of any dietary management. Finally, in a third group dietary treatment may be beneficial when phenylalanine concentrations are maintained sufficiently high to allow normal protein synthesis.

The duration of treatment is also controversial, and various centers have advocated terminating dietary restriction between 4 and 15 years of age.¹⁴ In a more recent study the age at which the diet was discontinued was not a factor in the child's ultimate performance. Rather, discontinuation of the diet was followed by a decrement in I.Q. of those children who had been under strict dietary control (blood phenylalanine less than 9 mg per 100 ml) but not of those whose blood phenylalanine had been maintained at higher levels.¹²

Maple Syrup Disease

Maple syrup disease is a familial cerebral degenerative disease due to a defect in branched-chain amino acid metabolism, and is characterized by a sweet, maple syrup-like odor in the urine. It was first described in 1954 by Menkes et al.¹⁴ The condition occurs in all races, with an autosomal recessive inheritance.

The disease is characterized by the accumulation of three branched-chain keto acids: alpha-ketoisocaproic acid (KICA), alpha-ketoisovaleric acid (KIVA), and alpha-keto-beta-methylvaleric

TABLE 2.—*Defects in Urea Cycle Metabolism*

<i>Disease</i>	<i>Enzymatic Defect</i>	<i>Clinical Features Accompanying Mental Retardation</i>	<i>Biochemical Findings</i>
Argininosuccinic aciduria ¹⁷	Argininosuccinase	Seizures, white brittle hair (trichorrhexis nodosa)	Elevated urine, spinal fluid argininosuccinic acid.
Citrullinuria ¹⁸	Argininosuccinic acid synthetase	None	Elevated blood, urine citrulline. Elevated blood ammonia after high protein meal.
Hyperammonemia ¹⁹	Ornithine trans-carbamylase	Intermittent coma, attacks of vomiting	Elevated blood ammonia.
	Carbamylphosphate synthetase ²⁰	Intermittent coma, cyclic neutropenia	Elevated blood ammonia.
Lysine intolerance ²¹	Unknown; defect in arginase	Intermittent coma, spasticity	Increased plasma lysine and arginine, increased blood ammonia.

acid (KMA). These are the derivatives of leucine, valine and isoleucine, respectively. In maple syrup disease a single gene defect involves more than one enzyme. It is likely that the enzymes affected in maple syrup disease have a common polypeptide chain which is under the control of a single gene. As a consequence of the defect, the three previously mentioned keto acids accumulate in serum and cerebrospinal fluid, and are excreted in large amounts.¹⁵ Plasma levels of the respective amino acids are elevated secondarily.

The structural alterations in the nervous system are similar to those seen in PKU, but more severe.

In most patients opisthotonos, intermittent increase in muscle tone and respiratory irregularities appear within the first week of life, with subsequent rapid cerebral deterioration. Severe hypoglycemia develops in about half of them.

As with PKU, a number of variants have been reported. In one type patients have intermittent ataxia, drowsiness and behavior disturbances. Another variant has been observed in a retarded child, while in the most recent described entity, the condition responded to thiamine.

Maple syrup disease is diagnosed by the characteristic odor of the patient and a positive 2,4-dinitrophenylhydrazine test on the urine. The ferric chloride test sometimes produces a navy blue color. Chromatography of the urine for keto acids, or of the serum for amino acids confirms the diagnosis.

As in PKU a diet containing restricted amounts of the inadequately handled amino acids—in this instance leucine, isoleucine and valine—has been used in treatment. For optimal results the diet should be initiated during the first few days of life, and frequent quantitation of the serum amino acids is necessary. A sample synthetic diet has been described.¹⁶

A few children maintained on such a regimen have been known to achieve a fairly adequate intellectual development.

Defects in Urea Cycle Metabolism

Five inborn errors in the urea cycle have been described, with one defect at each of the five steps in the conversion of ammonia to urea. They include argininosuccinic aciduria, citrullinuria, and two conditions termed hyperammonemia, the more common being due to a defect in the conversion of ornithine to citrulline. Congenital lysine intolerance is also associated with periodic ammonia intoxication, most likely due to interference by lysine with the enzyme arginase. These diseases have in common an autosomal recessive transmission, and a clinical picture highlighted by moderate to severe mental retardation, seizures, vomiting, and intermittent episodes of stupor or coma. In all of them the enzyme defect is partial, for complete failure of ureogenesis would be incompatible with life. Neurological symptoms are believed to result from chronic hyperammonemia, and restriction of protein in-

take to 1 to 2 grams per kg of body weight per day will often free the patient of symptoms. The conditions are outlined in Table 2.

Aside from the above diseases, hyperammonemia is also seen in chronic liver disease and in other genetic disorders whose biochemical basis is still unclear. These include a syndrome of familial protein intolerance, and intermittent hyperammonemia with abnormally high levels of ornithine in the blood and homocitrulline in the urine.²²

Histidinemia

Histidinemia, which may be a harmless metabolic variant, has been described in several children who presented with a variety of minor neurologic disturbances, such as delayed speech secondary to impaired auditory memory.²³ The condition is due to an interruption in the first step of the histidine catabolic pathway, the conversion of histidine to urocanic acid.

The diagnosis is made by the addition of ferric chloride to the urine, which results in the appearance of a permanent olive green color (Table 1). The diagnosis is confirmed by the elevation of histidine in blood, and by enzymatic assays. Treatment of histidinemia with a low histidine diet has been proposed, but in view of the uncertainty of the natural course of the disease, we have no way of judging its effectiveness.

Homocystinuria

Homocystinuria, which was discovered by Field²⁴ in 1962, is an inborn error of methionine metabolism manifesting itself by multiple thromboembolic episodes, ectopia lentis, and mental retardation. The incidence is second to that of PKU amongst the inborn errors of amino acid metabolism.

The metabolic defect is one of cystathionine synthetase, the enzyme catalyzing the formation of cystathionine from homocysteine and serine. As a result of the block, increased amounts of homocystine, and its precursor methionine, are found in urine and plasma. Two variants of the disease are now distinguished: in one administration of oral pyridoxine does not alter homocystine excretion, while in the other large doses of the vitamin (500 mg a day or higher) eliminate homocystine from plasma and urine.

The primary structural alterations in the disease are noted in blood vessels of all calibers.²⁵

In most there is intimal thickening and fibrosis, and both arterial and venous thrombosis is common in brain and various other organs. The relationship between the metabolic defect and the vascular changes is unclear.

The condition is transmitted in an autosomal recessive mode, Homocystinuric infants appear normal at birth and their early development is unremarkable until seizures, developmental slowing or cerebrovascular accidents occur between 5 and 9 months of age. Ectopia lentis has been recognized by 18 months, and is invariable in older children. Secondary glaucoma and cataracts are common. In the typical older child the hair is sparse and brittle, and there are multiple erythematous blotches. The extremities and digits are long, giving the pseudo Marfan's appearance. About half of the patients experience major thromboembolic episodes.

The diagnosis of homocystinuria is suggested by the appearance of the patient, and may be confirmed by a positive urinary cyanidenitroprusside reaction (Table 1). The test is also positive in the presence of large amounts of cystine and acetone.

Restriction of methionine intake lowers the plasma methionine of homocystinuric children, and eliminates the abnormally high excretion of homocystine.²⁷ Although the biochemical picture can be improved by these means, there is no evidence for clinical benefit.

Other Rare Metabolic Defects

Various studies have appeared in the literature describing a single family or a few patients with neurological disturbances associated with an abnormality in the amino acid pattern of serum or urine. Some of these conditions are listed in Table 3.

Several other disorders, often discussed together with the aminoacidurias, are manifested by intermittent episodes of vomiting, lethargy, acidosis and the excretion of ketone bodies. Many of these are detected by the purple color given to the ferric chloride reagent by large quantities of urinary acetone (Table 1). They are also included in Table 3.

This brief review has attempted to summarize our current knowledge with respect to the various disorders of amino acid metabolism. Although a number of other disorders still remain to be discovered, one suspects that the vast ma-

TABLE 3.—*Some Rare Defects in Amino Acid Metabolism Associated with Neurologic Symptoms*²⁶

<i>Disease</i>	<i>Enzymatic Defect</i>	<i>Clinical Features Accompanying Mental Retardation</i>	<i>Biochemical Findings</i>
Cystathioninuria	Cystathioninase	Retardation in some, but others normal.	Urine, brain cystathionine elevated
Hyperglycinemia (Ketotic)	PropionylCoA Carboxylase	Early ketosis, precipitated by protein intake, progressive extrapyramidal signs.	Elevated blood glycine. Severe ketosis after leucine load. Unusual ketone bodies.
Methyl Malonic Acidemia	Methylmalonyl CoA Carboxylase Mutase	Metabolic Acidosis, intermittent coma.	Ketoacidosis, increased excretion of methylmalonic acid, elevated glycine, ammonia.
"Sweaty Feet" Syndrome	Fatty acid Dehydrogenase	Lethargy, acidosis, striking urinary odor.	Excretion of butyric and hexanoic acids.
Isovaleric Acidemia	Isovaleryl CoA Dehydrogenase	Recurrent acidosis, coma, unusual body, urine odor.	Isovaleric acid in urine, serum.
Lactic Acidemia	Unknown	Recurrent acidosis, coma.	Accumulation of lactic and pyruvic acids.
Hyperprolinemia	A. Proline oxidase B. Pylroline-5-carboxylate dehydrogenase	Renal hypoplasia, deafness, seizures. (Some patients are normal)	Elevated plasma, urine proline.
Hyperlysinemia	Unknown	Hypotonia and seizures, but also in normal child.	Increased plasma and urinary lysine.
Hartnup's disease	Transport of neutral amino acids	Intermittent ataxia, rash, photophobia, intellectual disturbances, no mental retardation. Very rare in U.S.A.	Increased output of amino acids, indolic compounds. Intestinal transport of tryptophan impaired.
Hypervalinemia	Valine transaminase	Vomiting, failure to thrive, nystagmus, mental retardation.	Increased blood and urine valine. No increase in keto acid excretion.
Sarcosinemia	?Sarcosine oxidase	Mental retardation.	Increased blood and urine sarcosine, ethanolamine.
Hyperbeta-alaninemia	Beta-alanine-alpha-Ketoglutarate transaminase	Seizures commencing at birth, Somnolence	Plasma urine beta-alanine and beta-aminoisobutyric acid elevated. Urinary gamma-aminobutyric acid elevated.
Hyperalaninemia	Pyruvate decarboxylase	Intermittent cerebellar ataxia and choreoathetosis	Increased serum alanine, lactate, and pyruvate.
Carnosinemia	?Carnosinase	Grand mal and myoclonic seizures. Mental retardation.	Increased serum, urine carnosine, increased CSF homocarnosine.
Beta-Hydroxyisovaleric Aciduria and Beta-Methyl Crotonylglycinuria	?Methylcrotonyl-CoA carboxylase	Similar to infantile spinal muscular atrophy, urine smells like that of a cat.	Increased urine beta-hydroxyisovaleric acid, beta-methylcrotonylglycine.

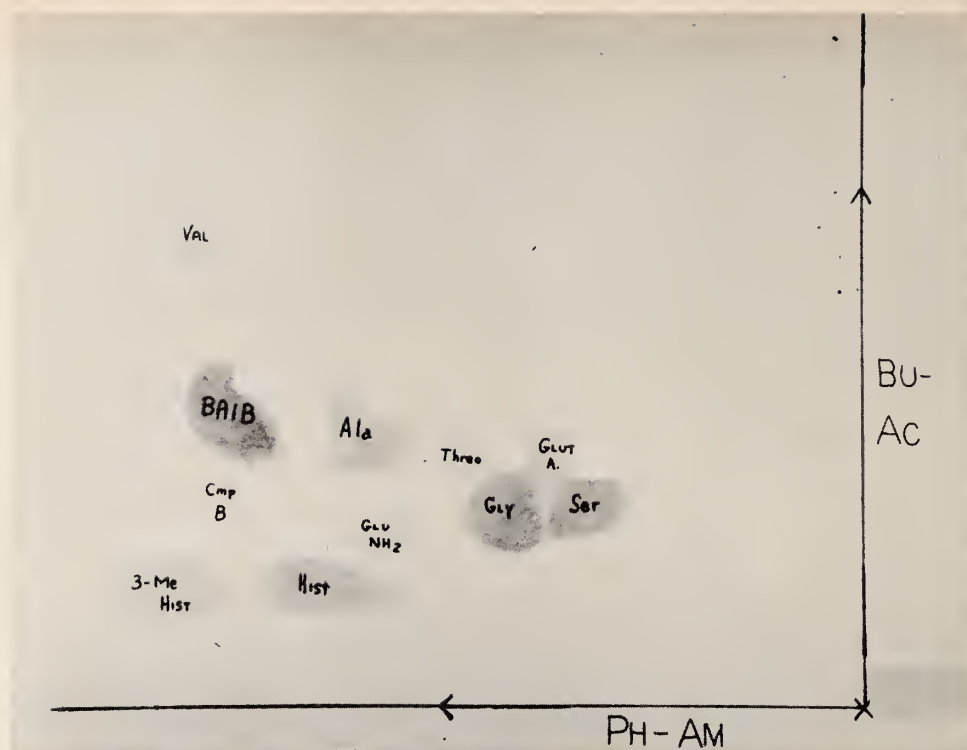


Figure 1.—Normal urinary amino acid chromatogram. An equivalent of 60 μ g creatinine was applied. Chromatography on Whatman No. 40 paper, developing solvents: butanol-glacial acetic acid-water (120:30:50) (BU-Ac), and phenol-ammonium hydroxide (200:1) (PH-AM). Amino acids visualized by ninhydrin spray. (Gly = glycine; Ser = serine; Glut A = glutamic acid; Threo = threonine; Hist = histidine; GluNH₂ = glutamine; BAIB = β -aminoisobutyric acid; 3-Me Hist = 3-methylhistidine; val = valine.) The subject excretes a large amount of BAIB, an asymptomatic metabolic variant.

jority of patients having a biochemical defect in this area of intermediary metabolism can now be diagnosed and classified, and possibly improved with the therapeutic armamentarium which we have currently on hand.

Diagnosis of Amino Acid Disorders

When a patient's neurological disease cannot be explained on the basis of a congenital or acquired defect of the nervous system, and especially when a like condition exists in the immediate family, the physician must consider the diagnosis of an inborn metabolic error. In many of these conditions the clinical picture is either nonspecific or has not yet been completely defined. The diagnosis is therefore made by demonstrating an abnormality of the chemical constituents in body fluids or tissues.

Urinary Screening Tests

For the routine clinical screening of aminoaciduria we advocate the use of three procedures (Table 1).

Ferric Chloride test: 3 to 5 drops of a 10 percent ferric chloride solution in 2 N hydrochloric acid are added to 1 ml of urine without previous acidification. The color change occurring immediately and over the subsequent 3 to 4 minutes is noted. The green color produced by urine containing phenylpyruvic acid fades within 30 minutes, while that produced by the tyrosine derivative, p-hydroxyphenylpyruvic acid, is even more transient. By contrast the olive-green color seen in urine from patients with histidinemia is permanent. The urine in maple syrup disease sometimes yields a navy blue color with this reagent. When ketones or salicylates are excreted, the urine gives a purple color after addition of ferric chloride. Phenothiazines and isoniazid produce a green color.

DNPH Test: To 1.0 ml of urine, 0.2 ml of a 0.5 percent solution of 2,4-dinitrophenylhydrazine in 2 N hydrochloric acid is added drop by drop. A definite yellow precipitate, forming within 1 minute, represents a positive reaction. This reaction is given by carbonyl compounds including acetone, and keto acids such as phenylpyruvic

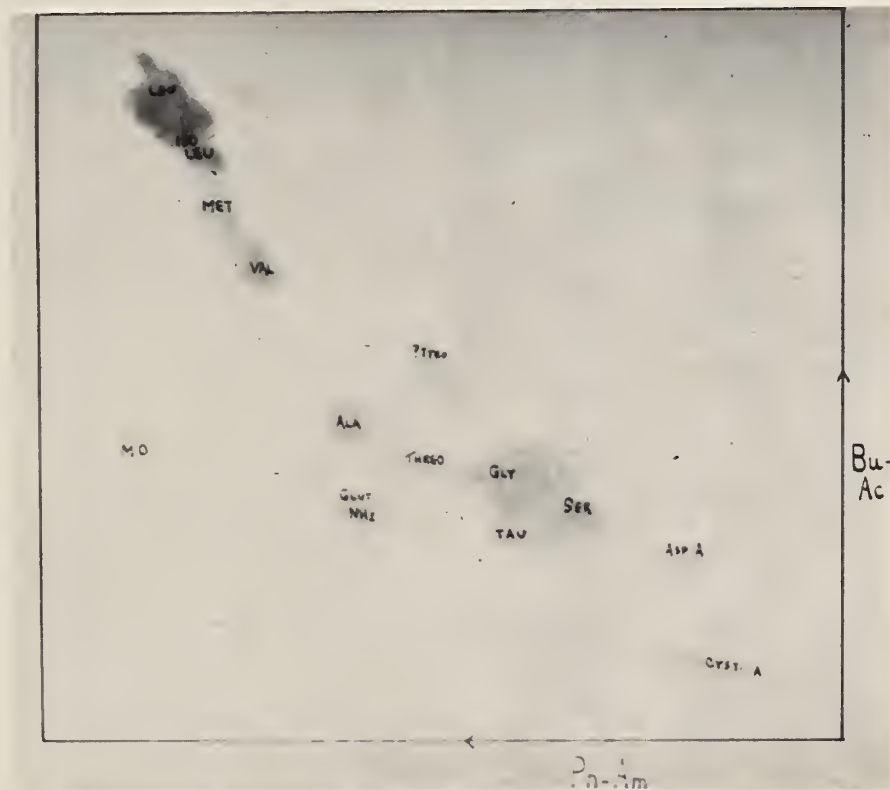
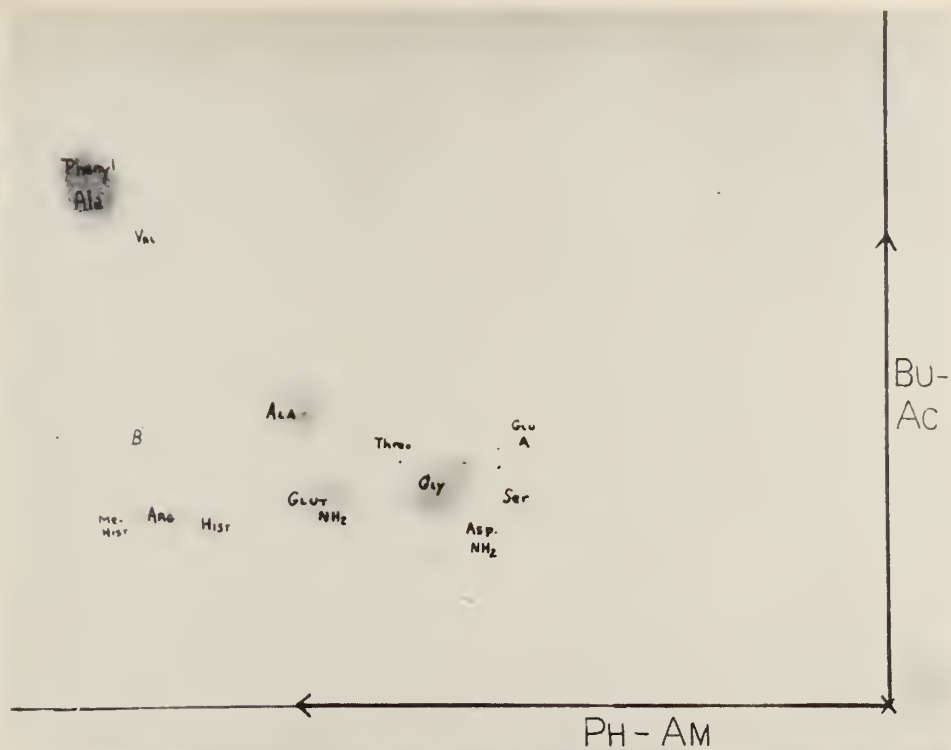


Figure 2.—Upper frame shows urinary amino-acid chromatogram in phenylketonuria. The conditions are the same as those employed for Figure 1. The spot representing phenylalanine is prominent in the upper left-hand corner of the chromatogram.

Lower frame is urinary amino-acid chromatogram in maple syrup disease. The three branched-chain amino acids are prominent in the upper left-hand corner.

acid, and the branched-chain keto acids excreted in maple syrup disease. Although a precipitate may form, the reagent is stable at room temperature for several months.

Nitroprusside-Cyanide Test: To 5 ml of urine, several drops of concentrated ammonium hydroxide and 2 ml of a 5 percent solution of sodium cyanide are added. After 5 to 10 minutes, a few drops of a 5 percent solution of sodium nitroprusside are added. A burgundy color represents a positive reaction. It is obtained in the presence of homocystine, cystine, and large amounts of acetone. The reagents are stable in plastic bottles for several months at ice box temperature.

In our experience more than 90 percent of patients with disorders of amino acid metabolism are detected by these relatively simple tests and by a reliable blood ammonia determination.† In the presence of a positive reaction further confirmation of the nature of the inborn metabolic error requires qualitative and quantitative chromatography and enzyme assays.

Qualitative amino acid chromatography is done by a number of hospitals and university centers, and in most instances is sufficient for diagnostic purposes. A commonly used procedure employs previously desalted urine, which is subjected to two-dimensional chromatography. A variety of acidic and alkaline developing solvents can be used to develop the chromatogram. Amino acids are visualized by spraying with ninhydrin. When normal urine containing 30 to 60 μ g of creatinine is chromatographed, the principal amino acids visualized are glycine, serine, alanine, histidine, glutamine, and lysine (Figure 1). Taurine and cystine are often lost when the urine is desalted, while glutamic acid indicates bacterial decomposition of glutamine. While traces of phenylalanine are detected in the urine of normal persons, a child with phenylketonuria excretes large amounts of this amino acid (Figure 2). In maple syrup disease the excretion of branched-chain amino acids is strikingly increased (Figure 2).

A method of urinary keto-acid chromatography employed by us²⁸ can be used to detect a number of metabolic disorders characterized by abnormalities in ketone excretion, notably phenylketonuria, maple syrup disease, and the hyperglycinemias. The ketone bodies are precipitated in the form of their 2,4-dinitrophenylhydrazones and subjected to uni-dimen-

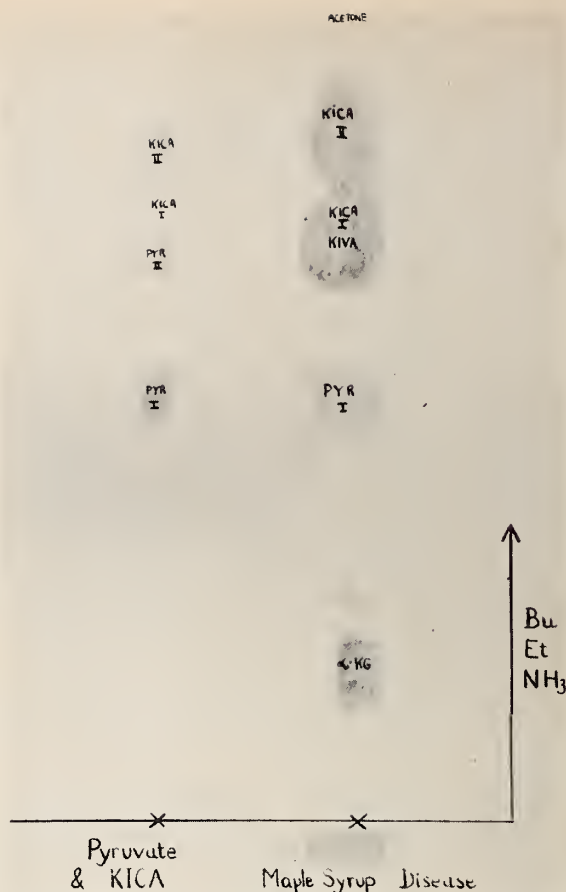


Figure 3.—Urinary keto-acid chromatogram in maple syrup disease. The two major spots represent the keto acid analogues of the three branched-chain amino acids. (KICA: alpha-keto-isocaproic acid; KIVA: alpha-keto-isovaleric acid). Developing solvent: butanol-ethanol-0.5 M ammonium hydroxide (130:20:50). Spots visualized by their natural color.

sional thin-layer chromatography. In maple syrup disease the two major spots represent the keto acid analogues of the three branched-chain amino acids (Figure 3). This procedure is available in a number of California institutions. Quantitative amino acid chromatography, which is performed by a California commercial laboratory, is less helpful as an initial screening device, and certainly more expensive and laborious. It can be done* on selected patients whose initial studies suggest a defect in amino acid metabolism. In most instances children should be put into hospital and their protein intake strictly monitored before this procedure.

Enzymatic assays are performed on liver and kidney biopsy material, and on fibroblast cultures derived from skin biopsy specimens. For this

†Dr. Samuel Bessman, Department of Pharmacology, University of Southern California.

*In a few California institutions; in Los Angeles by Dr. K. N. F. Shaw of Children's Hospital.

purpose the enzyme assays have to be well standardized, and referral to a center interested in a given disorder is necessary.

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ANTIBIOTICS IN PANCREATITIS

"I use antibiotics routinely in all patients in whom I make the diagnosis of pancreatitis. The infections I have seen associated with the pancreas are most commonly Gram-negative, and therefore I use a broad-spectrum antibiotic. Since the patient needs intravenous fluids anyway, I pick out one that can be given intravenously. Then the patient doesn't have to be stuck and have this bother during the rest of his illness. I commonly use tetracycline or Keflin® as the drug of choice. I do not use some of the antibiotics which in themselves may be associated with complications. Therefore I don't use Kantrex®, for example, as my initial antibiotic. Nor do I use chloramphenicol, which may be associated with other complications. I pick out a safe broad-spectrum antibiotic which can be administered intravenously."

—GEORGE L. JORDAN, JR., M.D., Houston
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Specialty Conference

Tetanus

Participants: WILLIAM L. NYHAN, M.D., PH.D., JAMES D. CONNOR, M.D., ROBERT N. HAMBURGER, M.D., JOHN H. KERR, D.M., F.F.A.R.C.S., AND JOE YOUNG, M.D.

Taken from the weekly Pediatric Grand Rounds held at the University Hospital of San Diego County, University of California, San Diego, School of Medicine, March 2, 1971

DR. NYHAN: * We have many things to show and tell this morning. We shall begin with the case presentation by Dr. Young.

DR. YOUNG: ** J. was a 12 year old Mexican boy admitted to Children's Health Center in San Diego with chief complaint of generalized rigidity. The history given was that a week, more or less, before admission the patient had cut both feet while playing on an old mattress. Three days before admission progressive generalized rigidity of the jaw, extremities and trunk developed.

Past history indicated that the patient probably never had had DPT immunization. On physical examination he appeared to have no respiratory distress. He had facial trismus and generalized rigidity of the jaw. The extremities and trunk were also rigid, and he assumed an opisthotonic posture. Careful examination of the skin revealed no lacerations or punctures, although there were many minor abrasions over the lower extremities and the chest.

*William L. Nyhan, M.D., Ph.D., Professor and Chairman, Department of Pediatrics.

**Joe Young, M.D., Assistant Resident, Department of Pediatrics, University Hospital of San Diego County.

Reprint requests to: Pediatric Immunology and Allergy Division, Department of Pediatrics, University of California, San Diego, School of Medicine, P.O. Box 109, La Jolla, Ca. 92037 (Dr. R. N. Hamburger).

Immediately a dose of 4,000 units of Hyper-Tet® (tetanus immune globulin, human) was injected intramuscularly and diazepam (Valium®) was administered intravenously until the spasms completely cleared. Treatment with penicillin, one million units every three hours, was begun at the same time. Also given at the beginning of treatment was 60 mg of phenobarbital, and this was repeated every eight hours.

The acute course lasted approximately one week. During this time the total amount of Valium per day peaked at 30 mg, given in 5 mg doses. Toward the second hospital week Valium by mouth controlled the spasms. By the end of the second week there were no more spasms and the patient was discharged 16 days after admission and approximately three weeks from the onset of disease.

Discussion

Dr. Connor* asked me to discuss some of the problems we had and observations we made, since I was with this patient most of the time he was in hospital. The usual incubation period for tetanus is 5 to 14 days. This child had received the cuts on the feet a week, or possibly

*James D. Connor, M.D., Associate Professor; Head, Division of Infectious Diseases, Department of Pediatrics.

as little as three days, before the development of symptoms. In general, the sooner the onset of symptoms the more severe is clinical tetanus.

Another perplexing factor was the site of infection. We really did not see any puncture wounds or lacerations on the feet or elsewhere. X-ray studies of both feet were negative for foreign bodies. Feeding the patient posed problems. For the first three days he was sustained by intravenous fluids. During the first two days when we did try to feed him even clear fluids in small amounts, trismus was triggered and laryngospasm ensued. By the fourth day of treatment with Valium, trismus had lessened and the patient was able to take clear fluids. By the end of a week he was eating a regular diet.

Spasms occurred about four times as often during the day as at night. We assume that this is because of the stimulation that occurs during the daytime, when even in an intensive care unit there is more activity and the patient was watching television. At night, from approximately midnight to 7 a.m., he had no spasms and we did not use any Valium. Results with Valium in this patient were impressive. He responded completely to as little as a 5 mg dose. More, at one moment he would be completely rigid, and then in the next, following a dose of the drug, he would become completely relaxed.

As this was the first patient with tetanus I had ever treated, my classification as to severity of the disease is not based on experience. I would consider the following factors in classification: (1) the spasms came only with stimulation; (2) the frequency of spasms was not great—the intervals were longer than ten minutes; (3) the duration of spasms was from 10 to 60 seconds; and (4) there was no impairment of the airway. Using these guidelines I would estimate that the patient fits the moderate category of tetany. Since his discharge the patient has done very well.

DR. NYHAN: Dr. Young, tell us what kind of criteria you used for the titration of this patient. How did you decide when he needed 5 mg of Valium?

DR. YOUNG: We calculated a total dose per day at 5 mg per kg of body weight, and this came out to 150 mg per day for this boy. Then we started with 5 mg initially and repeated it slowly until his rigidity disappeared and he became completely calm. The first time, it took approx-

imately 10 to 15 mg. Thereafter, when he had an attack of tetanic spasms, 5 mg was enough. Then we stayed at the 5 mg dose.

DR. NYHAN: How did you select the 4,000 units dose of Hyper-Tet?

DR. YOUNG: We got that from the Red Book,¹ which recommended anywhere up to 5,000 units.

DR. NYHAN: Thank you very much. The management of this patient has relevance to our rotation of residents to Mexico City. Tetanus is endemic in Mexico, and house officers working there should get experience in its management. I would like to turn this discussion over now to Dr. Connor, who is going to show a film and narrate it.

DR. CONNOR: We have prepared a three-minute movie on this patient to illustrate the condition and its treatment with Valium. He was very hypertonic. His rigidity was demonstrated here with sustained clonus following activation of the Achilles stretch reflex. At that time about eight hours had elapsed since his last dose of Valium. Then he was given 5 mg of Valium intravenously. The injection is painful. The material tends to flocculate upon mixing in a very small volume of intravenous fluid. Since it is painful the patient reacts, as demonstrated, with a spasm, and then, gradually at first, then very quickly, he relaxes. The post-Valium relaxation stage is very dramatically different from the rigidity which immediately preceded it. A desirable part of this type of therapy, especially in a mild case, is that it leaves the patient awake, conscious, and responsive.

DR. NYHAN: I was interested to see that during the examination in the film, following the treatment with Valium, the patient had a demonstrably soft abdomen and at a time when he still had some clonus. It has been my experience with patients with tetanus that one of the earliest signs of the return of tetanus following treatment, or the last sign to disappear as they are being effectively managed, is the tension and rigidity of the abdominal musculature. It is usually a useful sign, but it just didn't happen to be in this case, at least on the first day. We shall now turn the discussion over to Dr. Kerr, who is going to consider the management of tetanus.

DR. KERR: ° This was, I thought, a very nice demonstration of how well Valium can control mild to moderate tetanus.² At the other end of this

¹John H. Kerr, D.M., F.F.A.R.C.S., Visiting Assistant Professor, Anesthesiology Division, Department of Medicine.

scale, there is a 71-year-old man upstairs, weighing only about twice as much as this boy does, who received 360 mg of Valium over a period of about 12 hours. At the end of this time he was considerably more rigid than at the beginning and was having more in the way of muscle spasms. So general paralysis with curare was employed. While Valium will control the muscular symptoms in some cases, it will not work in all.

Prognostic Criteria in Tetanus

When tetanus is first diagnosed, the symptoms are often not fully developed, but it has proved prognostically useful to consider the rate of development of the disease. The most commonly employed indices of this rate are the incubation and the onset period.³ The incubation period is the time between injury and the appearance of the first symptom of tetanus; the onset period is that between the appearance of the first symptom and the first major spasm. Short periods of incubation (less than seven days) and of onset (less than 48 hours) are generally followed by more severe tetanus and vice versa.

The boy we are discussing had an incubation period which may have been as short as five days, though it was difficult to date it exactly because he had several minor injuries from any one of which he may have contracted tetanus. His onset period, however, was at least three days, because on admission he was complaining of trismus and stiffness rather than muscle spasms. From this you would have guessed that the course would be moderate rather than severe.

Classification of Severity

Classification is usually done in retrospect on the basis of the symptoms observed during the course of the disease.⁴ A case in which only trismus and rigidity develop is classed as mild. If there is dysphagia as well as muscle hypertonicity and perhaps mild spasms, the classification is moderate. If, in spite of treatment, muscle spasms which interfere with ventilation occur, the disease is severe.

Pathophysiology

Clostridium tetani is a Gram-positive rod which grows and produces its toxins only in regions of low oxygen tension. Wounds which are likely to become the site of clostridial growth in-

clude deep punctures in which necrotic tissue is present and wounds enclosing a foreign body. The tetanus toxin that causes muscle spasms (tetanospasmin) reaches the central nervous system by way of the nerves or the bloodstream, and probably by a combination of these routes. In the spinal cord it has been shown to affect the ability of the anterior horn cells to produce inhibitory postsynaptic potentials. Thus, the normal balance of excitation and inhibition in the final common pathway to the muscles is upset, excitation becoming preponderant. A good example of this effect was seen in the present case when the boy was stimulated before he had received Valium. The "mass reflex" seen [in the motion picture] after the knee was tapped represented an uninhibited response to the stimulus; the effects persisted (as clonus) and spread up the cord to involve other muscle groups in the absence of the normal modulating influences.

It is worth stressing that tetanus is not an infectious disease in the ordinary sense. People who are looking after patients with tetanus, provided they don't get cuts on themselves infected from the site of infection on the patient, will not catch the disease. I stress this because I recall one operating room superintendent who refused to allow a tetanus patient into her operating room for tracheostomy on the grounds that he was going to infect all the other patients. I also have been questioned by one or two nurses who were worried about catching the disease from patients.

Treatment

General Measures

To ensure that all clostridia are killed, treatment with either penicillin or tetracycline should be started as soon as tetanus is suspected. The focus of infection should be sought, and, if found, surgical debridement and excision should be carried out to prevent further toxin production. All patients with established tetanus should receive human anti-tetanus immunoglobulin, preferably before wound excision. Published series have cast some doubt on the usefulness of these measures, but, in view of the difficulty in predicting the likely course of the disease from the early symptoms, it is almost impossible to get a true assessment of any moderating effect that may be exerted by these general measures.

Muscular Hypertonicity

The trismus and increased muscle tone in mild cases of tetanus can usually be controlled adequately with Valium given either orally or parenterally. This is probably the agent of choice at present. Mephenesin and chlorpromazine are two other centrally active muscle relaxant and sedative drugs which have been widely and fairly effectively employed in this disease.

Dysphagia

The hypertonicity of the masseters which produces the "locked jaw" of tetanus is often accompanied by increased tone and incoordination of the swallowing mechanism, resulting in dysphagia. This symptom usually appears early in the course of the disease and may be demonstrated as an inability to swallow saliva so that the patient drools or spits it out, or has a tendency to cough or clear the throat after attempting to swallow. Dysphagia may lead to two particularly dangerous situations.

First, swallowed material may be directed into the larynx, which has intact sensation but whose motor innervation may be irritable. Glottic spasm, usually accompanied by a generalized muscle spasm, often results, so that the body's oxygen supply is cut off at a time when the need is greatest. Children, especially, become cyanotic almost instantly, and a dangerous level of hypoxia may be reached very rapidly.

Second, with persistent dysphagia inhalation of oral contents may lead to aspiration pneumonia. Therefore, if dysphagia develops orotracheal intubation should be carried out after the patient has been anesthetized with thiopentone and relaxed with succinylcholine. The muscle relaxation brought about by these drugs makes it possible to open the mouth even though trismus may have been severe. After endotracheal intubation, tracheostomy can be done at a convenient time, preferably under sterile conditions in an operating room and under general anesthesia. Emergency tracheostomy under local anesthesia is to be avoided because of the danger of inducing glottic spasm during manipulation of the trachea.

After tracheostomy, the inspired gas should be well humidified, regular and effective chest physiotherapy should be carried out, and every precaution taken to prevent lung infection. It is my

impression that first class respiratory care can more than halve the reported mortality rate of 70 percent in untreated cases.

Muscle Spasms

Muscle spasms in tetanus can be either localized or generalized and of varying severity. Sustained contraction of the muscles is exhausting, painful, and, when the respiratory muscles become involved, dangerous. Centrally acting muscle relaxants such as Valium and chlorpromazine will control the milder spasms, but these drugs seem less effective in controlling spasms than in relieving rigidity. If large doses are employed in an attempt to control severe spasms, there is a risk that over-sedation will lead to hypoventilation between spasms. In this situation, and when muscular spasms themselves interfere with ventilation, the treatment of choice is general paralysis with curare and intermittent positive pressure ventilation. The results have been better when it is used early in the course of the disease than after prolonged attempts with sedative agents.

Once curarization and ventilation have commenced, barbiturates such as pentobarbital may be used to induce mild hypnosis. Some form of sedation is probably desirable, for despite reassurance many patients who are paralyzed but conscious will be frightened. In some of the most severe cases, however, particularly in old people, the patients may become unresponsive and appear comatose for periods of one to three weeks during the critical phase of their illness. They recover consciousness during the recovery phase and appear normal except for amnesia. In these patients sedative agents should be kept to a minimum.

Because of the bitter experience of having adult patients die of pulmonary embolism in the recovery phase after very severe tetanus, it has been our practice over the last seven years to give anticoagulants to any patient who has required curarization and ventilation. We begin this therapy 24 to 48 hours after tracheostomy and continue it until the patient is fully mobile again. Pulmonary embolism is much commoner in patients with tetanus than in paralyzed patients with other conditions treated in a similar manner, and in some series it was the cause of death in 20 percent of the fatal cases.

Nutrition

Patients with mild tetanus may be fed orally but if dysphagia develops, nasogastric feeding is preferable. While inserting a nasogastric tube at another time entails a risk of inducing glottic spasm, we have found that it can be done safely and conveniently while the patient is anesthetized for tracheostomy.

The chief advantages of nasogastric over intravenous feeding are that the considerable caloric and fluid requirements can be satisfied cheaply and effectively over the two to four weeks that patients with moderate or severe tetanus usually remain dysphagic. In addition, since tube feedings normally contain milk, the incidence of peptic ulceration is considerably reduced. This complication has been quite common in some series and almost invariably fatal in severe tetanus. Paralytic ileus has been reported fairly frequently in association with severe tetanus, but it usually responds to intermittent gastric drainage followed by the installation of antacid and anti-cholinesterase agents such as bethanechol.

Sympathetic Overactivity in Tetanus

In our series,⁵ the mortality rate among patients with mild or moderate tetanus is well under 10 percent, but in the severe cases it has remained at about 40 percent in spite of adequate

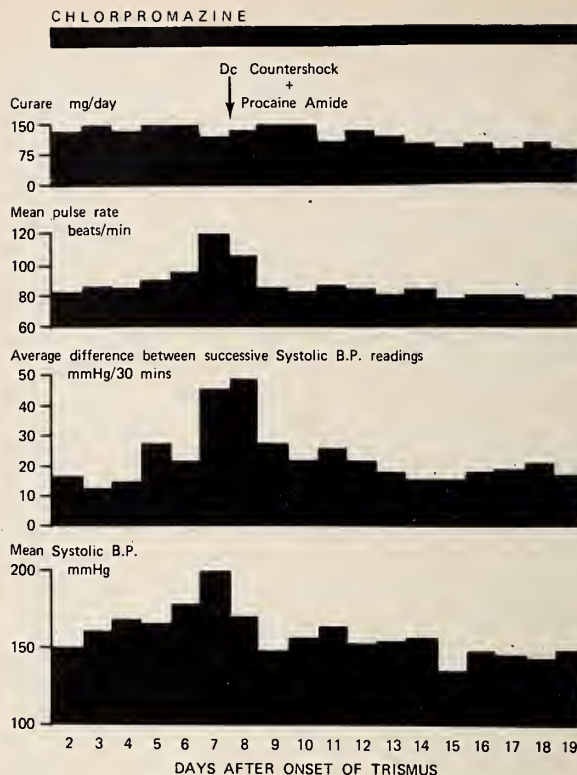


Chart 1.—Changes in 24 hour average systolic blood pressure (BP), variability of blood pressure, mean pulse rate, and curare requirements in a 58-year-old man with severe tetanus. The variability of BP is expressed as the average difference between successive half hourly readings of systolic pressure.

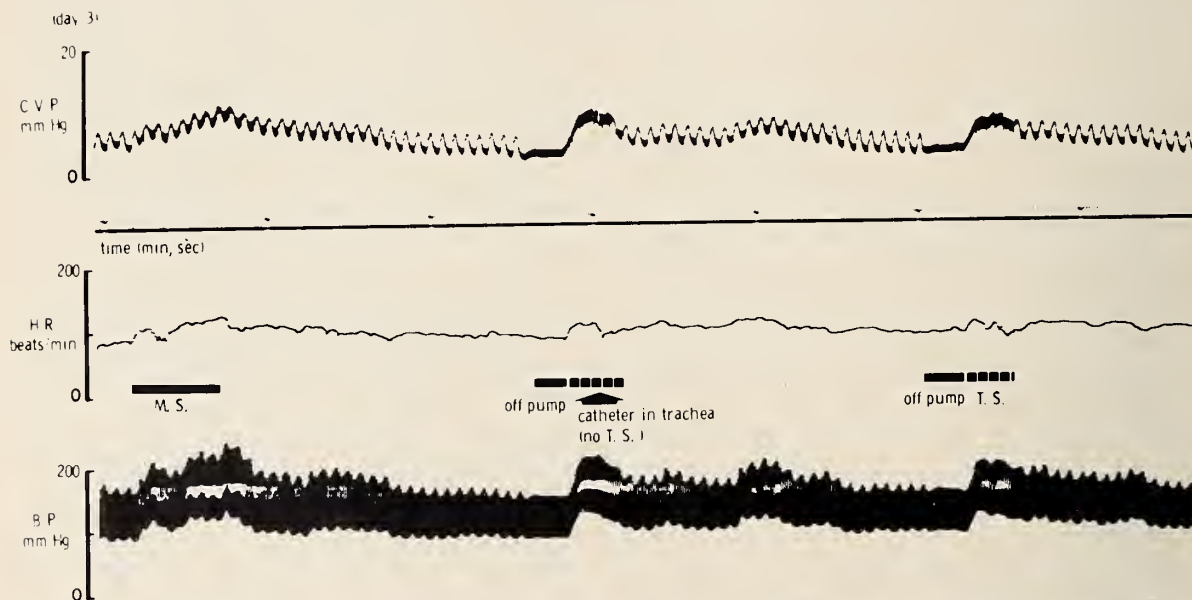


Chart 2.—Variations in central venous pressure (CVP) heart rate (HR), and arterial blood pressure (BP) in a 41-year-old man during oral suction (MS), insertion of catheter into the trachea (no suction), and tracheal suction (TS).

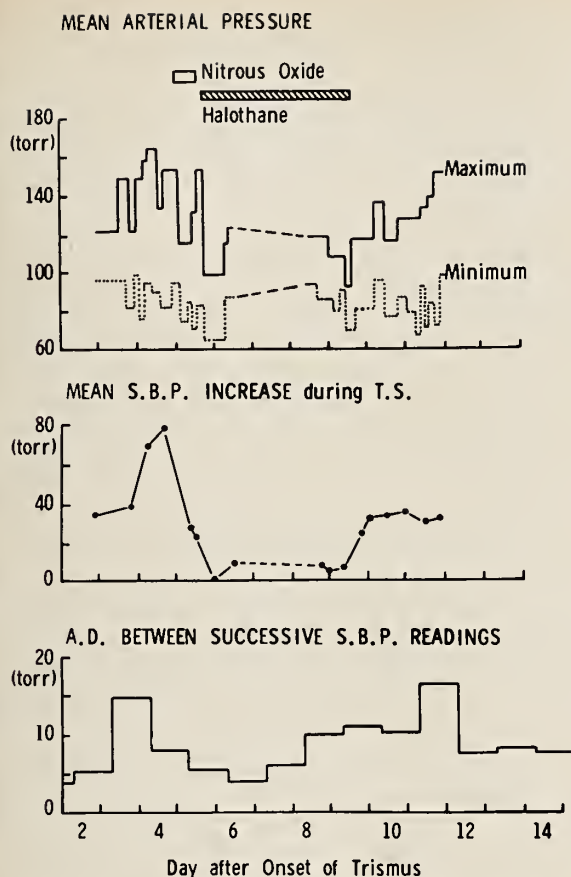


Chart 3.—Assessment of sympathetic nervous activity in a 9-year-old boy with severe tetanus. Changes in mean arterial pressure, mean systolic blood pressure (SPB) increase during tracheal suction (TS), and variability of the systolic blood pressure with time and therapy. Blood pressure variability is expressed as the 24-hour average difference (AD) between successive readings of systolic pressure.

control of the muscular symptoms, prevention of pneumonia, and other measures mentioned above. Postmortem examinations have been unrewarding, but a study of the clinical courses of patients with severe tetanus—both fatal and non-fatal—showed that in many cases there were features suggesting that the sympathetic nervous system was overactive. It is possible that tetanus toxin acts on both the anterior horn cells, causing the classical muscular symptoms, and the lateral horn cells. If inhibition within the sympathetic nervous system were blocked, exaggerated and incoordinated autonomic activity might be predicted.

Among the clinical features shown by patients with severe tetanus were the following:

- A temporary hypertension associated with

tachycardia (Chart 1), which occurred even if patients were being treated with doses of sedative agents such as chlorpromazine up to 600 mg a day.

- Increased variability of the blood pressure due in part to spontaneous changes in pressure and in part to exaggerated circulatory responses to stimuli. Among these stimuli was the procedure of aspirating secretions from the trachea (Chart 2). The cardiovascular response to tracheal suction paralleled the degree of cardiovascular instability and increased with increasing variability of the blood pressure, (Chart 3). The response to this stimulus is much more pronounced in patients with tetanus than in other paralyzed patients such as those with myasthenia gravis or acute polyneuritis.

Another autonomic stimulus which has been investigated is Valsalva's maneuver. In this maneuver, the increased intrathoracic pressure impairs transpulmonary blood flow, and the systemic blood pressure falls. The hypotension stimulates the baroreceptors so that sympathetic tone increases to restore the blood pressure. After release of the raised intrathoracic pressure, blood flow through the lungs resumes, and the blood pressure increases. There is normally an "overshoot" in pressure because of residual sympathetic activity, but in patients with tetanus the "overshoot" is exaggerated and prolonged (Chart 4). This is explainable on the basis of an irritable and underinhibited sympathetic nervous system and is the autonomic concomitant of the muscular "mass reflex" that was observed when the boy's knee was tapped.

- Other clinical findings that have contributed to the picture of an overactive and incoordinated sympathetic nervous system include high cardiac output with low arteriovenous oxygen content differences, day-by-day increase in systemic vascular resistance, profuse sweating in normothermic patients, and hyperpyrexia in the absence of infection.

- Metabolic observations have included high carbon dioxide outputs in paralyzed patients, raised plasma catecholamine levels, and increased catecholamine excretion.

Continued sympathetic overactivity is known to have deleterious effects, and an improved prognosis has followed the use of adrenergic

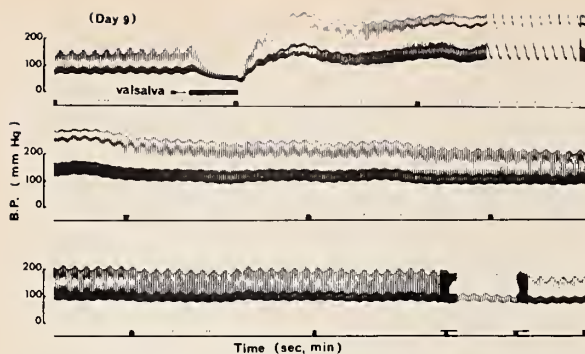


Chart 4.—Arterial blood pressure changes during Valsalva's maneuver in a 74-year-old man on the ninth day after the onset of trismus.

blocking agents in other conditions in which the sympathetic nervous system is overactive (pheochromocytoma and thyrotoxic crisis, for example). These agents have been used on a limited scale in patients with sympathetic overactivity in severe tetanus. The results were encouraging. To permit rational use of these agents and to deepen understanding of the autonomic involvement in this disease, continuous monitoring of cardiovascular variables is essential. The conventional quarter-hourly or half-hourly auscultatory blood pressure reading becomes insufficient in a situation in which the systolic blood pressure may fluctuate irregularly between 50 and 250 mm of mercury within a space of 5 minutes.

The Tetanus Unit

In view of the decreasing incidence of tetanus and of the increasing complexity of the methods used in managing it, in Britain and in France patients with tetanus from a fairly wide area are transported to specially designated tetanus units.⁶ These units are usually based on existing respiratory care units and are likely to treat several cases of tetanus each year. Expertise in handling this treacherous disease develops, and results of treatment have improved. The overall case fatality rate from the tetanus units in Britain was 22 percent for the decade up to 1968, and that for one of the largest French units was 33 percent for the period 1961 to 1964. In this country the New Orleans group, which also has a continuing experience with the disease, has reported a similar case fatality rate.

For the United States as a whole⁷ the case fatality rate remained at more than 65 percent in

both 1965-66 and 1968-69, the contrast suggesting setting up regional tetanus units in this country.

DR. NYHAN: Thank you very much, Dr. Kerr. I'd like now to request some comments from Dr. Connor.

Additional Considerations

DR. CONNOR: Dr. Kerr has given us a very lucid description of the treatment of patients with advanced clinical tetanus. It might be timely to draw a comparison between patients with severe disease and those with mild to moderate disease in relation to control and prevention of repetitive spasms.

In the past almost all the methods used included one or several drugs which, in addition to blocking or lessening spinal cord activity, also depressed cortical activity and activity in the centers of control of other vital functions, particularly respiration. Therefore, the physician was almost always dealing with a patient who was not only relaxed but also made semi-comatose or comatose. As a consequence the dangers of therapy may at times have been greater than those of the disease, since respiratory complications due to the inability to cough, handle secretions or swallow were not uncommon. The highly desirable effect of diazepam (Valium) in controlling spasms and hypertonicity without depression of cortical and other higher centers has made it the drug of choice in the treatment of clinically moderate tetanus. I would like to add that in my experience, as in Dr. Kerr's, if one is unable to attain a state of control of spinal cord activity over a fairly long period after the intravenous administration of Valium, and if increasing doses are required at shorter intervals, then the patient probably cannot be controlled with this drug. High doses, given at frequent intervals, may lead to respiratory depression and hypotension. Inability to achieve control with Valium is indicative of progressive and severe clinical disease. The total dose that one has to go to initially in determining whether or not the patient can be controlled with Valium is about 1 to 2 mg per kilogram of body weight, given in fractional doses. It is usually advisable to start with a fairly small dose intravenously, such as 2 to 5 mg, particularly when the patient has received other medications, especially barbiturates.

TABLE 1.—*Tabulation of Reported Cases of Tetanus in the United States in 1968 and 1969**

<i>Type of Wound</i>	<i>Cases with a Given Injury</i>	<i>Percent of Total Cases</i>	<i>Fatal Cases</i>	<i>Case-Fatality Ratio</i>
Puncture	87	29.3	55	63.2
Laceration	84	28.3	48	57.1
Miscellaneous	42	14.1	28	66.7
Abrasion	28	9.4	16	57.1
No Wound	22	7.4	13	59.1
Injection	20	6.7	15	75.0
Crush	10	3.4	5	50.0
Surgical	3	1.0	2	66.7
Dental	1	0.3	0	...
Total	297	100	182	61.3

*Excludes neonates, one person of unknown age, and cases with unknown outcome.

Passive Immunization

Another comment I would like to make bears on the question of passive immunization with hyperimmune tetanus globulin.⁸ There are now a number of studies which compare the efficacy of varying amounts of hyperimmune globulin (made in horses or other animals) to no antitoxin at all or to a small dose of antitoxin. Most of these studies support the opinion that antitoxin administered after tetanus has developed is not effective in reducing the morbidity or mortality of the disease. However, an occasional study has shown otherwise, and in my opinion it is wise to continue to use moderate amounts of the human antitoxin in all cases in the dose ranges mentioned by Dr. Young.

Prevention

Now, I would like to consider a few other aspects of tetanus which may be more important than treatment. The first of these is prevention by immunization. Immunization against tetanus is one of the most effective of all public health measures. The detoxified protein exotoxin of *Clostridium tetani* is almost always used in combination with a similarly detoxified protein toxin of the diphtheria bacillus, and these, together with a highly concentrated bacillary vaccine of pertussis, are given as injections three or four times during the early months or years of life.

One way to assess the efficacy of such immunizations and boosters is to look at the cases of tetanus occurring during a given period. Table 1 lists reported cases of tetanus occurring in a recent 24-month period in this country.⁷ Ninety-six percent of the patients had received no tet-

anus immunization, by history; 4 percent had received two or more injections, by history. Thus immunity after immunization is at least 95 percent effective. In groups such as the Armed Forces where immunizations are routine and boosters are regularly administered, statistical evaluation indicates an even higher order of protection. The mortality rate in the civilian cases, based upon the 1968-69 surveillance data, is approximately the same in the immunized as in the unimmunized. However, other data, published by Takos from Dade County, Florida, suggested that the mortality rate was significantly decreased in immunized patients in whom the disease developed.

Duration of Protection

Another common question regarding tetanus immunization is the duration of protective antibody levels in properly immunized persons. I think there is no direct answer to that question, since the measurement of antitoxic antibody in serum only allows the conclusion of presence of antitoxic antibody, for what is protective against a minor infection with the tetanus bacillus may not be protective at all against an infection resulting from massive crushing injury, or a long standing, deep puncture wound with persistent anaerobiosis. Therefore, it is usually recommended that the periods between re-immunizations be kept short enough to maintain adequate protection from the clinical disease throughout the interval. At present this period is thought to be five to ten years in cases where there are no injuries requiring an immediate booster.

Response to Boosters

Another question relates to the length of "immunologic memory" of the host in respect to primary immunization. In the past there were reports that a rapid secondary (booster) response could be attained several years after a primary series, and then later reports made this ten to fifteen years. Now we know that even after 20 years the booster response occurs just as rapidly as it does in a person who is only five years away from the primary series. With respect to the booster response the antibody which mediates adequate protection is dependably elevated after an interval of approximately five to seven days after the injections. If protection is required be-

fore that time, then one must resort to the use of passive immunization with antitoxin.

The administration of human antitoxin is certainly superior to the old method of using horse serum antitoxin, in two respects. The first is that there is no reaction to the single administration of human globulin antibody, and the second is that the homologous protein in the circulation persists over a much longer period than the heterologous protein in the horse serum. Adequate protection is conferred by the use of 200 to 500 units intramuscularly at the time of injury. In my opinion, in the case of a persistent wound which is complicated by development of non-viable tissue, it would be well to repeat this dose one or more times at ten-day intervals.

Use of Immune Globulin (Human)

DR. HAMBURGER: * I would like to expand on Dr. Connor's comments on the immunotherapy of tetanus. The toxin elaborated by *Clostridium tetani* has been known to have an extraordinarily high, selective affinity for the cholinergic terminals of nerves. That is why once the toxin has been bound, antitoxin is ineffective. Most of our knowledge of tetanus antitoxin is derived from animal studies, but with the availability of a safe preparation for human use, its *early* use in tetanus is mandatory, and its prophylactic use in wound debridement or in suspected cases is highly recommended.

The present tetanus immune globulin (human) is a solution of gamma globulin prepared from venous blood of humans hyperimmunized with tetanus toxoid. It is 25 times concentrated Cohn Fraction II, containing 165 mg per ml of immunoglobulin, predominantly Immunoglobulin G. Its use carries little of the risk of allergenic sensitization or serum sickness commonly encountered with horse-derived antitoxin. Where the horse serum antitoxin was cleared from the patient's bloodstream and tissues in 8 to 15 days, the TIG (human) has a half-life of 25 days. It persists in adequate concentration for a period long enough to protect adequately while active immunity is being induced. For prophylaxis in an unimmunized person, 250 units (1.0 ml) intramuscularly will provide the adequate protection of a serum level of 0.1 unit per ml for over three weeks. The first immunizing dose of tetanus tox-

oid (0.5 ml intramuscularly) should be given within that period. For therapy 3,000 to 6,000 units (12 to 24 ml) intramuscularly is recommended. When confronted with a patient with a wound, unless there is documentable evidence of two or more tetanus toxoid injections or of completed immunization against tetanus, the patient should be regarded as not immunized and the TIG (human) as well as a tetanus toxoid booster should be given.

Questions and Answers

Question: At what point in therapeutic management do you administer tetanus antitoxin?

DR. CONNOR: It has been shown that when you have a wound infected by *Clostridia*, there is often a lot of toxin in the tissue around the wound, and it would seem logical to give the immunoglobulin before the wound is debrided, for the debridement process may mobilize toxin. When no wound or locus of infection is found, you should still give antitoxin at the earliest moment.

Question: How often are you unable to find the causative lesion?

DR. CONNOR: In many cases no wound is uncovered by history or by examination. If you look at obvious wounds which are thought to be the source of infection, culture is productive 25 to 35 percent of the time in good laboratories; so it is more common not to find the organism by culture than it is to find it, even in significant injuries.

DR. NYHAN: I have one comment on the question of the wound. Certainly we often do not find a wound in a patient with tetanus. On the other hand, our experience would say that an all-out search should still be made to find it, particularly these days when more children than ever walk around barefoot. I am reminded of the girl we saw with severe tetanus who turned out to have stepped on a chicken bone which lodged between her metatarsals, and the skin healed over it. It has become a reflex with me to make x-ray examination of the feet of children with tetanus.

Question: How often do you see emboli as a complication to therapy? Which risk is greater, emboli or anticoagulants?

DR. KERR: All the pulmonary emboli I have seen have been in older patients. Perhaps children do not get this complication. It is probably more

*Robert N. Hamburger, M.D., Professor and Head, Pediatric Immunology and Allergy Division.

important to ensure that tetanus patients do not become dehydrated than to anticoagulate them. Apart from one episode of hematuria, we have seen no complications of the anticoagulant therapy as such.

Question: Is there any sign or symptom during the incubation period to warn you that you may be dealing with tetanus?

DR. CONNOR: I have seen delays in diagnosis of as much as 96 hours in patients in whom the initial presenting symptom was dysphagia, diagnosed as sore throat by a physician and treated with antibiotics. I have also seen cases with mild to moderate trismus going on for two to three days diagnosed as phenothiazine reaction or hysteria, then, with progression, diagnosed as tetanus. In the early stages, general hypertonicity and particularly tightness of the abdominal wall muscles anteriorly are helpful in diagnosis. Attempts to demonstrate trismus are also very helpful, for the patient may not know that trismus is present. Spasms induced by stimulation, without loss of consciousness, which are repetitive and spread to skeletal muscles should imme-

diately call attention to the possibility of tetanus. **Question:** Is a patient immune after he has had tetanus?

DR. CONNOR: No, he may not be immune as a result of the infection and the disease. Perhaps the toxin elaborated is not in sufficient amounts to immunize or it is tied up by receptors in the nervous system before it can be recognized by the reticuloendothelial system. Therefore, all patients who recover from tetanus should receive primary or booster immunization.

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THE WAXY SKIN IN SYSTEMIC SCLEROSIS

"The cardinal manifestation of progressive systemic sclerosis is the hard waxy skin. It's true that you sometimes have patients with progressive systemic sclerosis who do *not* have the hard skin, but by and large this is the way you make the diagnosis. The change in skin texture begins at the periphery of the body and progresses centrally. There is great variability in the speed with which it progresses. In some patients it just seems to gallop up the arms into the face. In others sometimes spoken of as having acrosclerosis—I probably should think of them as a separate group—it will remain below the wrist for 15 years and in fact, never advance beyond that."

—JOHN L. DECKER, M.D., Bethesda
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The Spectrum of Fungal Endocarditis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Dr. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* The case history of today's patient will be presented by Dr. Robert Carolan.

DR. CAROLAN:** This was the third University of California Hospital admission for this 51-year-old white man, a chemical engineer, whose complaints were fever and chills. At age 11 the patient was thought to have had rheumatic fever; however, at age 19 a diagnosis of ankylosing spondylitis was made. A murmur consistent with aortic insufficiency was discovered some time later and was felt to be related to the spondylitis.

Two years ago, the development of congestive heart failure necessitated replacement of the aortic valve with a Hufnagel prosthetic valve. The patient then did well until a month before this admission, when recurrent episodes of transient cerebrovascular ischemia and the development of a right lower quadrant visual field defect prompted his first admission here. Because he was felt to have recurrent emboli originating from the prosthetic valve, replacement of this device was advised. During his second admission the Hufnagel valve, which was found to have an adherent thrombus, was replaced with a valve fashioned with isologous fascia lata. During cardiopulmonary bypass, the patient received intravenous cephalothin prophylactically;

no antibiotics were given subsequently. He remained afebrile and was discharged without a heart murmur.

Two days following discharge his private physician noted systolic and diastolic aortic valve murmurs during a follow-up physical examination. Blood cultures were sterile. Over the ensuing three weeks chills and high fever developed, finally prompting the present (third) admission.

On physical examination, the patient was acutely ill and obviously disabled by a poker spine. The rectal temperature was 39.8°C (103.6°F), pulse 130 beats per minute; respirations 22 per minute and blood pressure 130/70 mm of mercury. The neck veins were flat and the lungs were clear. There was a grade 5 of 6 aortic systolic ejection murmur and a grade 4 of 6 decrescendo diastolic murmur along the left sternal border. Petechiae and splinter hemorrhages were present. The spleen was not palpable.

Following the initial work-up, administration of aqueous penicillin was begun intravenously (40 million units per day), methicillin (15 grams per day initially; later 12 grams daily), and streptomycin (1 gram per day). The subsequent isolation of a species of flavobacterium from four blood cultures prompted discontinuance of all these antibiotics and the initiation of ampicil-

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**Robert Carolan, M.D., Resident in Medicine.

lin therapy. The flavobacterium was sensitive to all antibiotics tested with the exception of cephalothin. On 12 grams of ampicillin per day, the patient's serum was bactericidal for the flavobacterium in a 1:8 dilution.

He felt better transiently, but fever and chills persisted and more petechiae developed on the mucous membranes. After 12 days of ampicillin therapy, sudden severe pain developed in the right leg with reduction of the pulses in that extremity. Two days later a right superficial femoral artery embolectomy was carried out and the excised clot contained a large mat of fungal material. Subsequent culture disclosed the presence of *Aspergillus ustus*. Amphotericin B was begun and cardiac operation was scheduled with a tentative diagnosis of aspergillus endocarditis. Two days before operation the aortic insufficiency murmur became greatly attenuated although congestive heart failure had not supervened.

At operation the aortic valve cusp was found to be perforated and there were large granular deposits on the undersurface of the valve and about the valve posts. Sponge pledges which had been used to approximate the apices of the cusps were also heavily involved in the same process. Histopathological examination revealed myriads of aspergillus organisms and subsequent cultures grew *Aspergillus ustus*. The fascia lata valve was replaced with a Wada-Cutter prosthetic valve.

The patient was maintained on amphotericin B following operation even though *in vitro* sensitivity studies indicated that the fungus was resistant to 10 µg per ml of amphotericin B. After two weeks the drug was discontinued because of deteriorating renal function and doubt that it was having any beneficial effect.

Over the next six weeks the patient had a number of episodes of hemorrhage from the right superficial femoral embolectomy site. A dacron graft was eventually required, but bleeding continued and when a thrombus formed at the site the graft had to be removed. Culture of the excised graft and numerous cultures of blood, sputum and urine were sterile. The patient was discharged, after a total of 78 days in the hospital, on chronic anticoagulation therapy.

Four days later he was admitted for the fourth time with rectal bleeding. No bleeding focus could be found on examination of the



Figure 1.—Arteriogram demonstrating obstruction of the popliteal artery. The upper arrow points to the site of arterial obstruction by the embolus. The lower arrow indicates the distal segment of the obstructed vessel. Collateral circulation about the upper tibia is apparent.

gastrointestinal tract, but anticoagulation was discontinued. During the week in hospital he was continuously febrile. Six blood cultures were negative and no new murmurs were noted. Once again he was discharged.

Five days later the patient died suddenly at home. At autopsy performed at U.C. Medical Center, numerous large clumps of vegetation were seen about the aortic valve ring and the prosthetic device. These contained myriads of aspergillus organisms. There were no metastatic foci of infection.

DR. SMITH: May we now see the x-ray films?

RADIOLOGIST: On the chest x-ray film the day before replacement of the fascia lata valve with the Wada valve, cardiomegaly and decided

TABLE 1.—Predisposing Factors and Responsible Organisms in Fungal Endocarditis

<i>Predisposing Factors</i>	<i>Responsible Fungi</i>
A. Disseminated Mycotic Infection	<i>Histoplasma capsulatum</i> (rarely <i>Aspergillus</i> species, <i>Blastomyces dermatitidis</i> , <i>Candida albicans</i> , <i>Coccidioides immitis</i> , <i>Cryptococcus neoformans</i> and <i>Phycomyces</i> species)
B. Intravenous Narcotic Abuse (Heroin; Paregoric)	<i>Candida</i> species (including <i>albicans</i> , <i>guilliermondii</i> , <i>parapsilosis</i> , and <i>stellatoidea</i>)
C. Impaired Host Defenses	<i>Candida</i> species most frequently <i>Aspergillus</i> species increasingly common (rarely <i>Histoplasma capsulatum</i> , <i>Torulopsis glabrata</i> , and <i>Paccilomyces</i> species)
1. Prolonged antibiotic therapy	
2. Intravascular portal of entry	
3. Cardiac valvular abnormality	
a) Bacterial endocarditis	
b) Open heart surgery, with or without valve prosthesis	

prominence of the ascending aorta were noted. Two days after valve replacement, cardiomegaly persists, there is a left lower lobe infiltrate, and several chest tubes are in place. Subsequently the heart diminished in size. The arteriogram done before embolectomy (Figure 1) shows an obstruction in the popliteal artery with considerable collateral circulation below the point of occlusion. The spine films demonstrate the "bamboo spine" and fused sacroiliac joints characteristic of ankylosing spondylitis.

DR. SMITH: We have chosen this morning not to discuss this patient's primary illness of ankylosing spondylitis, or its association with aortic insufficiency, but rather the occurrence of fungal endocarditis which was a complication of the operation for aortic valve incompetence. Dr. David Drutz of the Division of Infectious Diseases will discuss this patient's illness.

DR. DRUTZ: * Thank you, Dr. Smith. Although I plan to devote most of this morning's discussion to fungal endocarditis, it is important to note that this patient had bacterial endocarditis before aspergillus infection supervened. It is not widely appreciated that bacterial endocarditis and its treatment, or overtreatment, are among the factors predisposing to fungal endocarditis. The fact that a species of flavobacterium was the original infecting microorganism is of particular interest. These Gram-negative bacilli are not normal inhabitants of the bowel, but occur naturally in soil and water. There have been several instances of infection with flavobacterium following cardiovascular operation,¹ and flavobacterium endocarditis has been reported.² The potential role of flavobacteria in Gram-negative pneumonias

following the use of contaminated nebulizer equipment has also been emphasized.³ It is intriguing that this patient received prophylactic cephalothin therapy, because the flavobacter species subsequently isolated from his blood was sensitive to every antibiotic tested with the exception of cephalothin. Thus, although it is difficult to be certain of the portal of entry of the flavobacterium, the microorganism may well have been selected out by prophylactic antibiotic therapy.

Factors Predisposing to Fungal Endocarditis

Among the microbial agents capable of initiating endocarditis, fungi rank rather low. As shown in Table 1, there are three distinct settings in which fungal endocarditis tends to occur.

Disseminated Mycotic Infection. North American blastomycosis, coccidioidomycosis, cryptococcosis, aspergillosis, and mucormycosis have all been complicated by endocarditis on rare occasion.⁴ Valve involvement is generally only one feature of widespread infection and is usually unsuspected during life. Less unusual is the occurrence of endocarditis in histoplasmosis; at least 18 such cases have been reported.⁵⁻⁸ Although clinical findings of endocarditis may be prominent in these patients, *Histoplasma capsulatum* is difficult to isolate from the blood. Thus the diagnosis of histoplasmosis usually depends on isolation of fungi from other organs. It is of interest that meningitis, a particularly rare manifestation of histoplasmosis, has occurred in association with histoplasma endocarditis on at least five occasions.^{7,9} Although endocarditis may occur as one feature of disseminated candidiasis, this appears to be rare.¹⁰ More often candida

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endocarditis appears "to be the result of initial implantation of the organism on the heart valves, with subsequent hematogenous disseminated fungal infection."⁴

Intravenous Narcotic Abuse. Endocarditis is a well-recognized complication of intravenous heroin and paregoric abuse. We have seen cases following the use of amphetamines ("speed") intravenously. Fungi are relatively rare among the microorganisms causing endocarditis in addicts.¹¹ Nevertheless, fungal endocarditis does appear to occur in higher incidence in heroin addicts than in the general population.¹² In the absence of underlying valvular disease, such infections tend to involve the aortic valve. Fungi do not appear to share the propensity of staphylococci to invade the right side of the heart.¹³

It is not clear why narcotic addicts are particularly prone to endocarditis. Presumably the repeated injection of contaminated drugs through dirty skin with dirty needles produces frequent bacteremia or fungemia. Nevertheless, reticulo-endothelial mechanisms are normally highly efficient in sterilizing the blood. It is possible that the drugs also damage the heart valves in some as yet undefined manner.

Candida species (*albicans*, *guilliermondii*, *parapsilosis*, *stellatoidea*) have been responsible for virtually all reported cases of fungal endocarditis in narcotic addicts. Indeed, *aspergillus* endocarditis did not develop in one addict who was known to have repeatedly injected himself with cocaine heavily contaminated with *Aspergillus niger*.¹³

Impaired Host Defenses. Three factors in particular appear to hamper host defense against fungi and to predispose to fungal endocarditis: prolonged antibiotic therapy, intravascular portal of entry, and cardiac valvular abnormality.

- **Prolonged Antibiotic Therapy:** Alterations in normal bacterial flora attendant upon prolonged antibiotic use are well known. When there is underlying cardiac valvular disease, and particularly when a portal for entry of fungi into the bloodstream is provided, fungal endocarditis may result.

- **Intravascular Portal of Entry:** Any breach in the integrity of cutaneous or mucosal surfaces provides a portal whereby fungi may gain access to the circulation. Prolonged intravenous therapy provides direct access to the bloodstream from the skin, and fungemia, particularly candidemia,

has become a particularly common problem with the use of plastic intravascular cannulas for drug administration and hyperalimentation. Fungi are not the only microorganisms to invade the bloodstream in this situation, but antibiotic therapy tends to select them out. While candidemia can often be terminated by simple removal of the contaminated cannula,¹⁴ disseminated candidiasis may develop. In the presence of underlying valvular disease, endocarditis may result.

Cooper and his colleagues have investigated the roles of antibiotic therapy and valvular damage in fungal endocarditis.¹⁵ In their study, aortic insufficiency was produced surgically in 12 of 14 dogs. All animals subsequently received 3.2×10^7 *Candida guilliermondii* intravenously. Nine dogs with aortic insufficiency then received eight days of antimicrobial therapy—penicillin and streptomycin for five of the animals and tetracycline for four. At autopsy, three of the dogs which had received penicillin and streptomycin and one of those treated with tetracycline had candida endocarditis. Endocarditis did not develop in the two dogs with intact aortic valves or the three with aortic insufficiency but no antibiotic therapy.

- **Cardiac Valvular Abnormality:** The development of fungal endocarditis during the course of prolonged intravenous antibiotic therapy for bacterial endocarditis is a well-documented¹⁶ but generally unappreciated phenomenon. *Candida* species are the usual superinfecting microorganisms. We recently had a patient in who *Torulopsis glabrata* endocarditis developed during the course of penicillin and streptomycin therapy for enterococcal endocarditis. In the present patient, it is not clear whether flavobacter and *aspergillus* endocarditis coexisted from the outset, or the *aspergillus* invaded a valve previously infected with flavobacteria.

Fungal endocarditis is a well-recognized complication of valvulotomy procedures and an increasingly common complication of prosthetic valve replacement. Prophylactic antibiotic therapy is generally employed during such surgical procedures and it is likely that fungi are selected out in this way.

Although *Candida* species are most frequently responsible for fungal endocarditis in these circumstances,^{17,18} *aspergillus* species are an increasingly frequent cause of infection.¹⁹⁻²² In-

deed, up to 1957 there were reports of only four cases of aspergillus endocarditis in the literature.⁴ *Histoplasma capsulatum* has invaded a prosthetic valve on one occasion,⁷ and species of *Paecilomyces* have been implicated in two infections.²³ The present case has a particularly intriguing parallel in the literature. Mershon and his coworkers²⁴ described a patient with flavobacter endocarditis involving a fascia lata graft in a previously damaged posterior mitral valve leaflet. The patient died despite therapy with multiple antibiotics. At autopsy, *Aspergillus terreus* was present as a huge mass arising from the posterior mitral leaflet, and disseminated abscesses were present in nearly every organ. However, secondary foci of infection do not commonly develop when fungi invade a prosthetic valve.²⁵

There is no evidence that any particular prosthetic appliance is uniquely susceptible to fungal invasion. Infections have occurred on fascia lata grafts,²⁴ homografts,²⁶ Hufnagel valves²¹ and Starr-Edwards valves,²⁰ among others.

Clinical Features

The clinical features of fungal endocarditis generally mirror those of bacterial endocarditis. Even focal glomerular lesions have been reported.²⁷ Three points, however, bear particular emphasis.

Blood Cultures. When species of candida are the infecting agent, blood cultures are generally positive.⁴ In contrast, other fungi are rarely isolated from the blood, even when they are specifically sought. Indeed, the clinical manifestations highly suggestive of endocarditis in the absence of positive blood cultures should raise the possibility of fungal growth.⁴

Continuous bacteremia is an important feature of bacterial endocarditis; it reflects the continuous shedding of microorganisms into the bloodstream from an infected endothelial surface.²⁸ The reason that blood cultures are not consistently positive for fungi is not clear, but this phenomenon may reflect inadequacy of present culture techniques or the presence of extremely low titers of fungi in the blood. Approximately 10^2 bacteria are present per ml of blood in bacterial endocarditis;^{28,29} similar data are not available for fungal endocarditis. The importance of culturing large volumes of cerebrospinal fluid when attempting to establish the diagnosis of

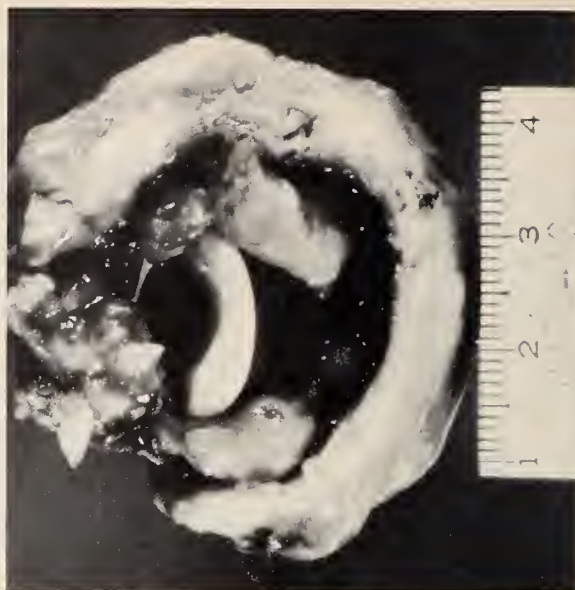


Figure 2.—Autopsy specimen of the excised aortic valve ring. For purposes of illustration, the prosthetic valve has been moved from its correct position. Large clumps of vegetation are apparent along the circumference of the valve ring.

fungal meningitis has been emphasized.³⁰ Perhaps a similar approach is indicated for the blood culture in fungal endocarditis. Akbarian³¹ has demonstrated the irregularity of positive blood cultures in experimental histoplasma endocarditis in dogs. Incisions 4 mm long were made in the aortic valve cusps of five dogs. Afterward 5×10^7 yeast-phase *H. capsulatum* injections were given intravenously and all the dogs developed endocarditis followed by widespread dissemination and elevation of histoplasma complement fixation titers. Of three dogs in which blood cultures were followed serially, one had only 3 of 37 and another only 5 of 35 positive blood cultures. The third dog had 10 of 22 cultures positive including nine positive in a row (a situation more reminiscent of bacterial infection). These cultures were obtained over a period of five to eight weeks.

Major Artery Emboli. No other feature of fungal endocarditis is so suggestive of this form of infection as a tendency for development of embolic occlusions of large arteries.^{4,5,17,18,32} Fungal vegetations on heart valves tend to become very large. The verrucae are soft and easily detached, producing large emboli. Figure 2 shows the size of the aspergillus vegetations on the aortic valve at autopsy in the case we are discussing today.

The importance of major embolic phenomena

cannot be overemphasized because surgical removal, pathologic examination and culture of embolic material can establish the diagnosis of fungal endocarditis. Both aspergillus³³ and histoplasma⁵ endocarditis have been diagnosed during life by excision and examination of an embolus from a large, accessible artery. Embolectomy in these circumstances is a diagnostic rather than a therapeutic procedure. Thus excision is warranted even though the embolus may pose no threat to the blood supply.

Changing Heart Murmurs. This is generally an overstated criterion for the diagnosis of endocarditis. A dramatic change in a preexisting murmur or the sudden development of a new murmur generally signals perforation of a valve cusp, rupture of chordae tendineae, or some other catastrophe. One does not await a change in a murmur before accepting a diagnosis of endocarditis.

In fungal endocarditis, changing murmurs may reflect the sheer bulk of vegetative mass at the valve orifice. In the patient we are discussing today, the disappearance of a previously obvious aortic insufficiency murmur before operation suggested partial occlusion of the aortic valve orifice in the absence of a lowered cardiac output from congestive heart failure.

Treatment

The role of antifungal chemotherapy is severely limited in fungal endocarditis. While histoplasma,⁸ cryptococcus³⁴ and candida³⁵ endocarditis have been cured with amphotericin B alone, it has become abundantly clear that valve excision is required in the vast majority of cases. When a prosthetic valve is infected, operation offers the only hope of cure—and even that hope is slim. Even though the aspergillus endocarditis of the present patient was diagnosed during life, the administration of amphotericin B and the prompt excision of the infected valve only extended his life for a few weeks. Ultimately aspergillus infection disrupted the new prosthetic valve. Nevertheless, although the prognosis for fungal endocarditis appears to be very poor, cure may be possible if diagnosis is established early, appropriate antifungal therapy is begun, and appropriate surgical measures are undertaken.³⁶

DR. SMITH: Thank you, Dr. Drutz. We will take time for one or two questions.

DR. HOPPER: * Do these patients present without fever?

DR. DRUTZ: The literature indicates that fever is a fairly regular manifestation of fungal endocarditis.³⁷

DR. MURRAY: † The big fungus problem in California is coccidioidomycosis. At least from clinical evidence this fungus is generally felt to be relatively resistant to amphotericin. I wonder if you have any sensitivity data about it that could provide guides for treatment.

DR. DRUTZ: Dr. Murray is referring to data which we have published concerning the amphotericin sensitivity of a variety of pathogenic fungi. A scheme for the therapy of systemic mycotic infections was based on this information in conjunction with serial measurements of the amphotericin serum concentration.³⁸ Basically, patients should receive amphotericin B in sufficient daily dosage to maintain serum levels of two times the minimal inhibitory concentration (MIC) of the infecting fungus. The strains of *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Cryptococcus neoformans* were sensitive to between 0.098 and 0.780 micrograms of amphotericin B per ml. We were able to maintain postinfusion amphotericin serum levels at least twice the MIC of these fungi with approximately half the daily dosage at present recommended (that is, 0.5 mg per kg of body weight per day, against the recommended 1.0 to 1.5 mg per kg per day). Treatment was conducted for an arbitrary period of ten weeks. The study indicated that the daily dose of amphotericin need not be increased to the point of frank toxicity before therapeutic response can be expected.

This approach has been tried in only one patient with coccidioidomycosis. We recently treated an elderly woman with a *C. immitis* paravertebral abscess by means of this method. The infecting fungus was sensitive to less than 0.5 mcg of amphotericin per ml. Published data on *C. immitis* indicates that its amphotericin sensitivity pattern is similar to that of *H. capsulatum*, with MIC's ranging from 0.5 to 1.0 mcg per ml.³⁹

I need not emphasize the dangers to the laboratory worker of manipulating *C. immitis*. At present there is no practical way for the routine

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hospital laboratory to measure the amphotericin sensitivity of coccidioides strains. Further, it is not clear whether a lowered dosage regimen would be feasible in patients with disseminated coccidioidomycosis, since these patients may respond poorly even with doses of amphotericin to the maximum of tolerance. However, the patient with the paravertebral abscess has done extremely well though never receiving more than 25 mg of amphotericin a day.

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Important Advances in Clinical Medicine

Epitomes of Progress -- Allergy

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Allergy. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Allergy which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Allergy of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

Lung Disease from Contaminated Air Coolers

HYPERSENSITIVITY ALVEOLITIS (HA) is a potentially fatal immunological reaction in the alveoli and alveolar ducts resulting from the inhalation of organic dusts by a person already sensitized by previous, usually prolonged and heavy exposure to the dust. It has been postulated that everyone is susceptible in much the same way that serum

sickness can be induced in anyone, although the amount of antigen necessary to trigger the reaction varies greatly among individuals. The disease has been most often related to occupational exposure to organic dusts as, for example, in farmers (exposed to moldy hay), mushroom workers, sugar can processors, pigeon breeders, and the like.

Symptoms vary from mild or severe "flu" syndrome with cough, chest pain, fever, chills, and myalgias, to severe pulmonary decompensation with dyspnea secondary to restrictive disease and diffusion defects. Vital capacity is decreased and wheezing is an inconstant feature. Interstitial pneumonitis and diffuse nodular infiltrates are seen in chest x-ray films. Serum obtained during the active process contains precipitating antibodies to the offending agent, and latex fixation

tests may be positive. Alveolar damage may be considerable and lead to extensive interstitial fibrosis.

HA has recently been reported in office workers exposed to an air conditioner whose filter was contaminated with a thermophilic actinomycete similar to the organism whose spores are responsible for farmer's lung disease, and in others exposed to home humidifiers also contaminated with a thermophilic actinomycete. Such reports suggest that HA may be more widespread than was previously believed. Prompt diagnosis is important because the prognosis grows worse with continued exposure. Although adrenocortical steroids are useful during the acute process, ultimate success depends upon ending of exposure to the dust responsible.

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Weiss WI, Tourville DR, Luedemann GM, et al: Hypersensitivity pneumonitis due to contamination of a home humidifier. *J Allergy* 47:113-114, Feb 1971

Enzyme-Containing Detergents as a Cause of Allergic Disease

SHORTLY AFTER THE INTRODUCTION of proteolytic enzymes from *Bacillus subtilis* in laundry detergents in 1967, reports began to appear of respiratory and nasal symptoms in workers exposed to high concentrations of the enzyme dust, including sneezing, rhinorrhea, wheezing, dyspnea and fatigue. These typically showed a biphasic pattern, with choking and cough beginning immediately after exposure and lasting a short time, followed in six to eight hours by more severe symptoms. At first, recovery was complete by the next day, but as exposure continued the symptoms became correspondingly more lasting.

Pulmonary function and gas studies showed that in addition to obstructive lung disease a reduction in carbon monoxide transfer occurred.

All workers who have symptoms following exposure to the enzymes give strongly positive wheal and flare reactions when skin tested with the enzyme known variously as alcalase, Maxatrase or subtilisin. However, a significant number who have no symptoms on exposure also react to skin tests, as do some persons who have never been exposed to the enzyme.

How much of a hazard the home use of enzyme containing detergents presents is not yet known. So far there have been only a few reports of nasal irritation. However, prolonged use in the home may lead in time to a significant amount of clinical sensitivity. It has been postulated that all persons may become sensitized given a sufficient exposure. Moreover, persons deficient in serum alpha-1 antitrypsin may be susceptible to the direct toxic effects of the proteolytic enzymes.

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Bee Sting Allergy

ALLERGIC REACTION TO BEE STING KILLS more people than snake bite. Of 460 documented cases of deaths from venomous creatures, 229 (50 percent) were due to bee stings. The honeybee accounted for 124 (27 percent) deaths, two-thirds of which occurred within one hour and 96 percent within five hours. Usually the patient had had reactions to previous bites.

Twenty-six hundred non-fatal reactions to bee sting were categorized as follows: 347 patients (13 percent) had local immediate reactions; 421 (16 percent) had slight general reactions with hives or itching of other parts of the body; 1135 (44 percent) had more severe generalized hives

and itching; 630 (24 percent) had severe generalized life-threatening reactions with unconsciousness, dyspnea or throat swelling; 73 (3 percent) had delayed reactions including hyperglobulinemia thrombocytopenic purpura, bloody diarrhea, nephrotic syndrome, hepatorenal syndrome, and CNS involvement (EEG changes, peripheral neuropathy, polyneuritis, transverse myelitis). Serum sickness reactions have been noted as late as ten days after a sting. Infection at site of sting is common, especially after stings by yellow jackets, wasps or hornets, which unlike the honeybee are scavengers.

The diagnosis is made primarily by history; however, skin testing, although not infallible, is confirmatory and should be performed with titration, increasing concentrations of extracts to determine the concentration to be used in hyposensitization. A refractory period of falsely negative skin tests may exist as long as three weeks after a sting. False positive skin tests are not infrequent. Hyposensitization injections are of value in reducing both local and systemic reactions. Duration of hyposensitization treatment has not been established. However, current thinking is that it should continue for at least five years with the injections being given every one to four months after a maximum dosage has been achieved.

Prompt emergency treatment is very important and persons known to be sensitive to hymenoptera should carry an emergency kit at all times. The stinger and venom sac of a honeybee should be scraped off completely with a fingernail, for it takes 2 to 3 minutes for the sac to empty. Epinephrine is by far the drug of choice, and should be injected both at the site of the sting to delay absorption, and elsewhere for systemic effects. Not quite as effective but more convenient for emergency kits are the inhalers containing epinephrine. Sublingual isoproterenol is no longer recommended, as it may worsen shock from peripheral vasodilation because of its beta-adrenergic effect. Antihistamines are also useful in the initial therapy and steroids may be of value later. A tourniquet should be included in every kit.

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Mites in House Dust

RECENTLY THERE HAVE been many reports concerning the possibility that house dust allergy is caused by pyroglyphid mite sensitivity. Evidence of this association has been based on history, finding the mites in homes, puncture skin tests, leukocyte histamine release, passive transfer and relief of symptoms by hyposensitization with mite extracts.

In contrast, Kawai et al have reported that while leukocytes of some house dust reactors release histamine in the presence of mite extracts, others do not.

In addition, Hosen has warned that insect extracts themselves contain histamine and can produce a wheal by either puncture or intradermal test.

Mites are probably an important cause of house dust allergy but other factors may also be involved. Further studies will be necessary to clarify the situation.

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Association of Air Pollution With Asthma

ASTHMA HAS TRADITIONALLY been associated with airborne pollutants from natural sources such as pollens and mold spores, and symptoms are believed to be mediated by allergic mechanisms. Nonspecific irritants may also produce asthma in

susceptible persons. Chemical air pollutants may produce decreased respiratory flow rates in persons dwelling in communities with air pollution, and in particular in patients with chronic respiratory disease. Admissions to hospital because of asthma are more frequent for residents of the more polluted sections of urban areas.

There are two major forms of air pollution: sulfur dioxide-particulates and photochemical smog. Both forms can cause increased airway resistance and interfere with the clearing mechanism of the bronchi. SO_2 is irritating, and can paralyze ciliary action, stimulate mucus production and cause bronchospasm and edema. Similar effects can be produced by ozone and NO_2 in photochemical smog.

The frequency of admittances to hospital for asthma increase the night of and the day following an increase in air pollution. In Japan, United States military personnel had to be evacuated from the Tokyo-Yokohama area because of pollution-induced asthma which responded poorly to bronchodilators. When petroleum refineries began to operate in Yokkaichi, Japan, there was a pronounced increase in asthma among local residents. In the acute air pollution episode in Donora, Pennsylvania, 87 percent of the asthmatics became ill, compared with 43 percent of the town's general population.

Experiments in guinea pigs indicate chemical air pollutants may contribute to allergic asthma. Ozone, NO_2 , and SO_2 enhanced antibody production to nebulized albumin and pre-exposure to the pollutants increase the experimentally induced dyspnea with antigen aerosols.

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Insulin Allergy

INSULIN PREPARATIONS generally contain mixtures of bovine and porcine insulin which are antigenic in man. Within a few months of the initiation of insulin therapy, circulating antibodies to insulin may be detected. Normally these antibodies are in low concentration, have low insulin-binding capacity and are of no clinical significance. Insulin resistant diabetes is generally associated with high levels of insulin-binding antibodies of the IgG class. IgA, IgM and IgE antibodies may also be found in diabetic sera.

Allergy to insulin has a spectrum of reactions including the frequent local reactions (5 to 30 percent of insulin-treated patients), generalized rashes, serum sickness and anaphylaxis. The skin sensitizing or P-K antibody to insulin is thought to be in the IgE class and is decidedly elevated in patients with anaphylactic sensitivity to insulin. This sensitivity can be partially or completely blocked by production of high levels of IgG blocking antibodies which in turn may lead to insulin resistance. These antibody interactions have many similar features to conventional allergy injection treatment for inhalant allergies and to the protective effect of specific IgG globulin in desensitization in penicillin allergy.

There are a number of steps which may be taken in managing patients with severe insulin allergy: (1) The brand or species of insulin used can be changed; (2) patients may be switched to oral antihyperglycemic agents; (3) insulin with structural modifications such as dealanination, may be used; (4) insulin therapy can be continued with hopes of producing a protective or blocking antibody. This protective effect may later be lost if insulin is discontinued.

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Air Cleaning Filters and Inhalant Allergy

SINCE THE DISCOVERY that the inhalation of air-borne particles is responsible for certain respiratory diseases, efforts have been directed toward removing or blocking these particles from the air breathed by susceptible persons. Highly effective filtering devices are available. They are known as electrostatic precipitators or high efficiency particulate air (HEPA) filters, and they can remove particles under one micron (μ) in diameter from the air entering the filters. Thus, pollen grains (15 to 30 or more μ), mold spores (2 to 50 or more μ), and probably dust and most animal danders can be readily blocked by such filters.

They are used most efficiently in clinical situations by incorporation into adequately designed central air conditioning units. The residence or place of work can then be kept closed in extremes of temperature. Additional helpful measures include the use of odor adsorbents (activated charcoal) and humidifiers.

Portable units for individual rooms have not been proved to be clinically effective.

All filtering devices have these inherent disadvantages when employed as therapeutic devices:

- They cannot magically remove all particles from the air.
- They can filter only the air that is presented to them.

Clinical improvement may be only partial even with the employment of the best units under optimal conditions. There is evidence, however, that the longer the patient can remain in a filtered environment, the less he suffers from his inhalant caused allergic reaction.

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Allergy and Serous Otitis Media

SEROUS OTITIS MEDIA associated with allergic rhinitis is a common cause of decreased hearing in children. The basic defect in this disorder is obstruction of the eustachian tube and accumulation of serous fluid or mucus in the middle ear. When air is prevented from reaching the middle ear, there is impairment of function of the tympanic membrane with conductive hearing loss.

Earache may be present along with a feeling of fullness in the head. Occasionally there is sudden onset of hearing loss and no complaint of pain or discomfort. The first sign may be inattentiveness in school or failure to pass a routine hearing test.

While no single cause can be implicated for all cases of serous otitis media, a large number of children will have nasal eosinophilia, a positive family history of allergy, positive skin tests for sensitivity, allergic rhinitis, or some other symptoms of the atopic allergic state.

Long term management requires proper diagnosis and treatment of any underlying allergic state. An allergy investigation may be of great value. No single method of treatment is always effective. Oral decongestants and antihistamines, environmental control with removal of house dust and animal danders, hypoallergenic diets with removal of specific food allergens, and desensitization to clinically indicated dusts, pollens, and molds may all be of value in therapy.

For the more intractable cases non-responsive to thorough allergic management, surgical intervention including the removal of obstructing adenoid tissue may be indicated. Whatever the cause of the problem, bilateral myringotomy with insertion of polyethylene tubes often produces an immediate dramatic improvement in hearing.

J. GARLAND STROUP, M.D.

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Current Status of Immunoglobulin E (IgE)

WHILE QUANTITATIVE measurements of serum IgE levels are not diagnostic of the allergic state, the great majority of persons with elevated IgE levels manifest allergic symptoms. A rare individual with low serum IgE may have proven allergy. In addition, serum IgE levels have been shown to be greatly elevated (thousands of ng* per ml) in parasitic infestations. The mean serum IgE level in non-atopic persons as determined in several laboratories varies from 143 ng per ml to 248 ng per ml with ranges (in non-atopic adults) from 19 ng per ml to 950 ng per ml (mean \pm 2 standard deviation).

Serum IgE is unique in having the widest range of all the immunoglobulins. Levels between 2 and 36,000 ng per ml have been reported. The half-life of serum IgE is about two and a half days in contrast to cell-bound IgE which persists for several weeks.

IgE does not normally cross the placenta and most newborns do not produce significant quantities of IgE. The lymph nodes of the gastrointestinal and respiratory tracts appear to be the principal areas of IgE production. Maturation results in increasing IgE levels throughout childhood paralleling IgA development. At all ages there is wide variation in IgE levels. In allergic children (with ragweed hay fever) the serum IgE level was found to be inversely related to age of onset.

Although the serum IgE level did not correlate with the symptom index in ragweed hay fever patients, a small rise in serum IgE was noted during the ragweed season in untreated persons. After hyposensitization therapy this rise did not occur.

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*ng: nanogram or 10^{-9} gram

Alpha-1 Antitrypsin Deficiency

NORMAL HUMAN SERUM inhibits the activity of proteolytic enzymes. Approximately 90 percent of this activity as measured by trypsin-inhibiting capacity is attributed to the alpha-1 globulin fraction of the serum and is termed alpha-1 antitrypsin.

Inherited deficiency of alpha-1 antitrypsin is associated with a high frequency of early onset, lower lobe emphysema which might be the result of the autodigestion of pulmonary tissue by the breakdown products of white blood cells and alveolar macrophages. Alpha-1 antitrypsin deficiency should be considered in the differential diagnosis of bronchial asthma and other chest diseases of young adults.

Whether slight to moderate deficiency of alpha-1 antitrypsin predisposes to chronic obstructive lung disease is still unresolved.

The diagnosis is made by finding a low level or absence of alpha-1 globulin on paper electrophoresis and confirming this by measurement of the serum trypsin-inhibiting capacity by chemical or immunological means.

LAWRENCE STRICK, M.D.

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Disodium Cromoglycate in the Treatment of Bronchial Asthma—Further Clinical Trials

FURTHER INVESTIGATION of disodium cromoglycate (cromolyn sodium) has confirmed previous reports of its efficacy in the treatment of bronchial asthma. (See Epitomes of Progress, Calif Med 112:40, June 1970.) The drug is administered as

a powder for inhalation and appears to have a protective effect in bronchial asthma by inhibiting the release of mediator substances. It has no bronchodilator, anti-inflammatory, antihistaminic or antiserotonin activity and is of no value in the relief of an acute bout of asthma.

When disodium cromoglycate is available generally for clinical treatment, indications for its use would be (1) as a prophylactic therapy before anticipated, unavoidable exposure to allergens, and (2) in severe chronic bronchial asthma of the extrinsic type unresponsive to the usual modalities of treatment.

LAWRENCE STRICK, M.D.

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The Familial Nature of Milk Allergy

THE FAMILIAL NATURE of milk allergy (milk intolerance other than that due to lactase deficiency) is receiving increasing attention. Gerrard points out the frequency with which he was able to demonstrate unsuspected milk allergy in parents of milk-allergic children. Seventeen percent of mothers and 7 percent of fathers had various symptoms caused by milk, but in only one instance had it previously been recognized as the culprit. Milk allergy could be demonstrated in only 1 percent of controls. Forty-six percent of siblings of milk-allergic children were also allergic to milk. Gerrard's data suggested that when parents of a milk-sensitive child had a second child, the chances it would also be sensitive to milk were 1 to 2.

In a recent exhibit on food allergy the reviewer found that in 90 families where a child was allergic to milk, there were 53 instances in which a parent also gave evidence of milk allergy. In seven of these 90 families, milk allergy had appeared in three successive generations and in one instance in four successive generations.

The usefulness of this information lies in the rewards to be had from searching for unrecognized milk allergy in both parents and siblings of a recognized case. A surprising number of instances of chronic respiratory symptoms (cough, rhinitis, sinusitis), headache, musculoskeletal pain, fatigue and other manifestations of the allergic tension-fatigue syndrome may thus come to light.

WILLIAM C. DEAMER, M.D.

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Young EJ: The allergic tension-fatigue syndrome. *Calif Med* 112: 46, Jun 1970

Nose Drop Habituation

EXCESSIVE AND CARELESS use of sympathomimetic amines for prolonged periods may lead to a clinical syndrome in which the dominant complaint is nasal stuffiness. Efficient mucosal vasoconstriction can be effected through oral medication. Consequently, nose drops are very rarely indicated and when used should be restricted to a few days' course under strict supervision.

Allergists frequently see patients with pronounced nasal congestion who, unknown to their physicians, have been using a nasal solution for long periods, even months. They unwittingly are creating, to a large degree, the condition they are treating. Physicians should select an effective oral medication as the treatment of choice in cases of acute nasal congestion.

E. JAMES YOUNG, M.D.

REFERENCE

Efficacy and abuse of nasal medication: A review (Editorial). *Ear, Nose & Throat Monthly* 44:75, Jun 1965

Clinical Use of Transfer Factor

TRANSFER FACTOR (TF) is a substance of unknown chemical identity which resides in the dialysable fraction of disrupted human peripheral blood leukocytes and which can passively transfer specific cellular immunity from a sensitized donor to a non-sensitive recipient. It has a molecular weight under 10,000 and clinical trials indicate that it is essentially not toxic. It is not immunogenic and in the passive transfer of cellular immunity it has a considerable advantage over intact white blood cells in that it cannot cause graft-vs.-host reactions. The amount contained in the leukocytes present in approximately 50 ml of blood will confer systemic immunity after injection into a normal person. TF from a donor highly sensitive to purified protein derivative can confer skin test reactivity lasting for as long as two years. The duration of any protective immunity conferred by TF will almost certainly be considerably shorter and depend upon the specific conditions for which it is used.

Because of the growing awareness that cell-mediated immunity is an essential defense against serious viral and fungal infections, interest in the potential clinical value of TF is increasing. It is currently being evaluated as a therapeutic agent in severe viral infections such as generalized vaccinia or disseminated herpes zoster. It is also being tested as a prophylactic therapy in conditions of impaired cellular immunity such as Wiskott-Aldrich syndrome. It does not appear to be able to restore cellular immunity in certain lymphoproliferative disorders such as Hodgkin's disease. Initial trials in patients with lymphopenic agammaglobulinemia have been disappointing.

V. A. MARINKOVICH, M.D.

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Levin AS, Spitzer LE, Stiles DP, et al: Wiskott-Aldrich syndrome, a genetically determined cellular immunologic deficiency: Clinical and laboratory responses to therapy with transfer factor. *Proc Nat Acad Sci* 67:821-828, Oct 1970

Excessive Use of Sympathomimetic Nebulizers in Asthma

BECAUSE OF THEIR ABILITY to furnish immediate and great symptomatic relief, sympathomimetic aerosols tend to be excessively used by asthmatics. The convenience offered by the recent introduction of gas-propelled nebulizers and devices to disperse micronized particles has increased the frequency of abuse. The concurrence of an increase in asthmatic deaths with the introduction and increased use of sympathomimetic nebulizers strongly suggests that over-utilization can be fatal.

Some asthmatic patients become refractory to isoproterenol aerosol following excessive use and then develop unremitting bronchospasm which is not relieved by other therapeutic procedures. Relief occurs only when use of the aerosol is discontinued.

Patients who have status asthmaticus with ventilation-perfusion abnormalities may have a paradoxical decrease of blood O₂ saturation when treated with isoproterenol while subjectively experiencing relief of asthmatic symptoms.

Patients should be given specific directions for the use of these nebulizers, and be warned about the dangers of excessive use. These devices should be kept under the control of the parents and children denied free access to them.

THOMAS L. NELSON, M.D.

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Doubtful Correlation Between Asthma and Worms

THE OVA OF AT least one of three worms, predominately *Ascaris lumbricoides*, were reported found in the stools of 198 out of 201 patients with asthma (Tullis, in *The New England Journal of Medicine*, Feb. 1970). The author of the report

concluded that these intestinal parasites can cause asthma. Three out of four subsequent letters in the correspondence section of the same journal took issue with the report. The writers pointed to the inadequate controls; questioned the need of more than three stool examinations in 51 percent of the patients, and more than 19 examinations in 14 percent; and cited the lack of change in the course of asthma when similar parasites were removed in their patients. Physicians with experience in endemic areas of intestinal parasites in Nigeria, West Cameroons, and Southern Iran found no relation to asthma, but one correspondent thought there was a relation in parts of India.

The first report to examine the validity of a high causative relation between asthma and par-

asites was presented at the American Academy of Allergy's meeting in Chicago in February 1971. The stools of 123 allergic and non-allergic patients at the Mayo Clinic were studied. No *Ascaris*, *Strongyloides*, or *Necator* were found. The authors of the report asked: Could the high incidence of parasites in Tullis' study, 91 percent of which were reported as *Ascaris*, have been due to pollen grains or fungal spores mistakenly identified as *Ascaris* eggs?

HAROLD S. NOVEY, M.D.

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EDITORIAL

An AMA Constitutional Convention

OCCASIONALLY SOMEONE steps forward and points clearly to what must be done, to an action which if taken and carried through successfully will almost certainly create a new and better order of things. Dr. Wesley W. Hall's bold and unexpected proposal that the time has come for the American Medical Association itself to hold a constitutional convention is a suggestion which is clearly in this category. It rings true. It could without doubt create a new order of things in health care. It is a suggestion which should be carried out, and this done with all deliberate haste.

A half century ago things moved more slowly and were much less complex. The AMA, structured as it was and still is, was then able to provide real leadership for medical practice, medical education and even public health. These were the days of some of its greatest accomplishments. But now the pace of change has become vastly more swift in both medicine and society, and the AMA organizational structure and machinery has nowhere nearly been able to match this swiftness of change and challenge. The result has been an abdication of leadership. Too many times the AMA has been simply inadequate in responding to the needs of both the profession and the society it serves. Attesting this has been the proliferation of scientific specialty societies and a considerable number of socially, economically and politically oriented professional organizations, all outside of the AMA; and within the AMA itself there has been a disturbing record of reluctant reaction to the *fait accompli*, rather than of innovative and imaginative action which might serve to direct the

course of events. The enemies and detractors of organized medicine have been watching this growing weakness with more than a little satisfaction for quite some time.

This is perhaps a uniquely opportune moment for the AMA to undergo organizational change and renewal. It is becoming obvious that society has not been able to solve the present day problems of health care without the help of the medical profession, although it has tried hard to do so. Planners in public health and elsewhere have failed. The consumers have been given their chance to try and they too have not succeeded. And the efforts of politicians to find political solutions have been enormously costly, relatively unproductive for the money spent, and generally have created more problems than they have solved. What should have been obvious from the beginning is now just beginning to be perceived: If health care plans and programs are to work and be satisfactory, both the providers and consumers must be involved in the planning and be satisfied with the plan to be carried out. Since it is they who render many of the services, physicians not only are among the key providers of medical care but are also key consumers in that they play an important role in determining how much of what resources are to be consumed. It is now certainly opportune and perhaps even incumbent upon organized medicine to play an effective role as a partner in finding workable solutions to many problems in health care, and a more effective organizational instrument is clearly needed to play this role.

It is suggested that the AMA constitutional convention should reexamine at least the following:

- The purposes of the AMA with respect to whether it should now become more action oriented than resolution oriented, and whether its role should be primarily active or reactive on the health care scene.
- The constituency of the AMA and whether it should be the advocate of only physicians, and if so which physicians, or whether its constituency and advocacy should also in-

elude the sometimes forgotten patient, the public, and other health care professions, medical education and public health.

- The decision-making processes of the AMA for short-range and long-range policy and action with particular consideration of the relation of these processes to the swiftness of professional and social change as it is today and may be anticipated in the next few decades.
- The fact-gathering and the information mechanisms of the AMA upon which scientific, social, economic and political policy and action decisions are made, and whether or not these are accurate and sufficient.
- The organizational structure and machinery for action of the AMA and whether or not these are capable of effectively furthering the association's aims both internally and externally.
- The governance of the AMA and its relationship to its members, its other constituencies if any, other professions in the health field, and public and private health care agencies.

Wesley Hall's suggestion offers a timely opportunity for renewal in the AMA and the chance for that body to play an enormously effective role in the significant years ahead. This opportunity must not be passed up.

—MSMW

Tetanus – The Role of Diazepam in Therapy

A NONFATAL CASE of tetanus in a 12-year-old boy with no previous history of tetanus toxoid injections is presented as the subject of the Specialty Conference in this issue of CALIFORNIA MEDICINE. The present annual incidence of this disease in the United States is only about one case per million population, and a gradual decline in both incidence and mortality rates has occurred over the last 20 years.¹ The age group from 10 to 19 years is especially favored by the statistics, since it has the lowest incidence of any age group in the United States, as well as the lowest case-fatality ratio (16 percent).²

Any potential improvement in the therapy of a frequently fatal disease is certainly welcome. The dramatic effects of diazepam on the rigidity and spasms of tetanus have been emphasized in the Specialty Conference and by other observers.³ Though its exact mode of action is unknown, diazepam appears to depress stimulatory influences of the brain-stem on spinal motor-neurons. Since the major effect of tetanospasmin, the neurotoxin of tetanus, is to block inhibitory influences that act on motor-neurons, diazepam might produce its effect by restoring a more favorable balance between excitatory and inhibitory influences. Regardless of its mode of action, the drug produces a desirable sedative effect, does not produce respiratory depression even when administered in high dosage, and seems superior in its muscle relaxant effects to other tranquilizer drugs, such as chlorthalidoxepoxide, meprobamate, and chlorpromazine, which have also been used in the treatment of tetanus.

Despite the above desirable properties, the effect of the inclusion of diazepam in the treatment of tetanus cases in the United States has not been sufficiently studied to allow any firm conclusions as to its influence on case-fatality ratios of this disease, which remains highly lethal especially for neonates and persons over 50 years of age (in these age groups more than three of every four patients die¹). The outcome of a case of tetanus depends on many factors of variable importance, and the effect of a specific variable may be difficult to establish except by the analysis of a large number of cases.^{1,4} Neither retrospective epidemiologic analysis nor a prospective clinical study of tetanus cases in the United States to evaluate the effect of diazepam on case-fatality ratios has yet been reported. A relatively small effect might be anticipated, however, since patients with frequent paroxysmal spasms that are triggered by both endogenous and exogenous stimuli are unlikely to respond satisfactorily to diazepam, and the treatment of choice in such cases is the induction of total paralysis with curare-type compounds and the provision of total respiratory support. The skill with which these maneuvers and their complications are managed will doubtlessly remain the major determinant of the outcome of severe cases.

It would be unfortunate if the dramatic clinical effects of diazepam led to an under-emphasis of the need for continuous and conscientious at-

tention to the patient, or to a disregard for the importance of other aspects of therapy. Tetanospasmin is presumably slowly metabolized from its binding sites in the nervous system and probably does not cause permanent structural damage. The objectives of therapy are to provide continuous supportive care to the patient while this event is taking place, and to prevent additional toxin from reaching the nervous system by the prompt administration of antitoxin, surgical excision of infected foci, and the use of antibiotics.

Antitoxin is inactive, and antibiotics are unreliable against spores of *Clostridium tetani*. Since the disease does not induce natural immunity, concurrent active immunization with tetanus toxoid is also indicated. Such immunization is particularly important when the infected site cannot be identified and surgically excised, as is illustrated by the case reported upon herein and nearly 7 percent of all cases in the United States.¹

The usefulness of diazepam as an adjunctive agent in the management of moderate or mild tetanus cases seems clearly established, but the significance of this drug on the mortality of tetanus among cases in this country has yet to be established.

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Inborn Errors of Metabolism

IT IS NOW NEARLY seventy years since the first publication of Garrod's studies on alkaptonuria¹ opened the field of human biochemical genet-

ics. It is of some interest for the history of medicine and science that these beginnings were clinical, with the careful observations of his patients by a scholarly physician. Garrod coined the term *inborn errors of metabolism* in the title of his book.²

These disorders are relatively rarely encountered. However, from the beginning they have been of significance far out of proportion to their incidence. It was from the study of inherited disorders of amino acid metabolism that the idea was first conceived that one gene determines the structure of an enzyme protein.² It was also in this context that the concept of genetic determination of human variation was first clearly expressed.^{1,2} Elsewhere in this issue of CALIFORNIA MEDICINE, Menkes has reviewed the status in 1971 of the disorders of amino acid metabolism. It is clear that these disorders continue to contribute to our understanding of health and disease.

The rate of discovery of new diseases promises continued excitement in this field. Recently, this has been particularly true for anomalies in the metabolism of the branched chain amino acids, a field of inquiry that was opened by Menkes with his description of maple syrup urine disease. Many of these disorders present with a picture of overwhelming illness very early in life, and if they are undiagnosed or untreated the patients seldom survive the neonatal period. These findings have focused attention on the newborn intensive care unit as a place where more metabolic diseases may be waiting to be discovered than in institutions for the mentally retarded.

The types of methodology employed in this field are changing too. Most of the early discoveries in the inborn errors of metabolism depended on the fact that amino groups react with ninhydrin to produce a readily detected purple color. This is the fundamental principle of the detection of amino acids whether by chromatography on paper or thin layer or by the automatic amino acid analyzer. It is probably true that the major proportion of what can be discovered using the ninhydrin reaction has already been discovered. On the other hand, in the catabolism of most amino acids one of the earliest steps results in the loss of the amino group. Therefore, inborn errors of the subsequent metabolism of these amino acids might make up the majority of such disorders. Their detection

would require the appreciation that compounds are accumulating behind an enzymatic block that do not stain with ninhydrin. Laboratories active in this pursuit now rely heavily on the gas chromatograph. We have found that an automatic organic acid analyzer is also useful, but we have had to construct this ourselves. An almost indispensable, but very expensive, item in a modern laboratory for the study of inborn errors of metabolism is a gas chromatograph linked to a mass spectrometer. This instrumentation has already quickened the pace of discovery.

Phenylketonuria (PKU) has been considered in detail by Menkes. This disease provides a rather comprehensive model for other inborn errors of metabolism. The fundamental defect, in phenylalanine hydroxylase, is known, as is the autosomal recessive mode of inheritance. Definitive diagnosis is quite readily made, although it is not as easy as it might have seemed five years ago. Experience indicates that there are a number of hyperphenylalaninemias which differ significantly from classical PKU. Variation of this type is becoming clear in virtually all of the inborn errors of metabolism.³ It is what one would expect. We can extrapolate from the genetic variation that codes for over 100 different hemoglobin proteins. There could be a similar degree of variation in primary structure for any protein in the body. In the case of enzymes, more than a few of these variants may lead to metabolic disease. Effective treatment is available for those diagnosed. This is not as easy, either, as it might have appeared theoretically. However, it is clear that patients diagnosed in the newborn period and managed properly, with sufficient phenylalanine to meet its requirement as an amino acid essential for growth, but essentially no more, end up with an impressively normal intelligence. Screening programs are now active in most states for the detection of every patient with PKU in the first days of life. The program in California is one of the best.

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A Critique

The California State Plan For Health

TO THE PHYSICIAN engaged in the private practice of medicine, the recently approved California State Plan for Health is met with mixed emotions. Those of us who were concerned with the development of the required document were aware that it was necessary to fulfill federal requirements for funding comprehensive health planning activities under P.L. 89-749 in our state.

Those who drafted the plan believe California's document is good in comparison with other states' plans, but also perhaps a somewhat premature exercise. The plan is an effort to deal with the multitude of problems pertaining to health in our state. It does help to identify major barriers to the achievement of certain goals and some methods of overcoming these barriers.

We should recognize that an opportunity was given to the most concerned people—physicians, planners, researchers, consumers—to present their "bit," and to have some input. Theoretically conclusions were derived from 240 position papers, some 4000 recommendations, and over 400 pages of record. Through the democratic process, many meetings and hearings were held. It is difficult to estimate the cost of the hearings, meetings, and position papers in terms of dollars and man-hours of time. But from these meetings and hearings, one would expect the conclusions and recommendations of the report would reflect those documented opinions and reports. Unfortunately on some issues one might say, "They listened, but they didn't hear."

One of the primary deficiencies in the state plan is the lack of accepted input from the private practitioners of medicine and dentistry. A second

criticism is that the plan represents a number of unorganized and undocumented opinions by many who never take care of a patient, and who add to the mix of the report from their diverse interests and backgrounds. Unfortunately, too, many recommendations are totally inconsistent or are based on assumptions and beliefs whose validity has not been established—for example, “mandatory maintenance of competence.” A non-medical planning organization has no role in assuming this kind of responsibility since it is incompetent to do so. Or again, only the profession itself can perform “peer review,” and we have already assumed this responsibility in medicine.

The plan does have some good points. For example, the section on Mental Health was rewritten several times, and is most praiseworthy. A recommendation under Manpower calls for a review to determine what should be the appropriate mix of physician specialists. And the plan does propose to establish priorities in conjunction with local and area-wide groups.

So let us consider the California State Plan for Health as a start and not the final one, as we approach solutions to the multitude of problems pertaining to health care in our state.

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Of Nurses and Physician's Assistants

NURSES USUALLY do not like to be cast in the role of “physician’s assistant,” and those who are attempting to define the function of the “physician’s assistant” do not think of casting this role as that of a nurse. Yet if things keep going the way they seem to be, there is likely to be less difference between these roles than some might think. To be sure, a nurse is more apt to be thought of as a woman and the physician’s assistant as male. But in these days this sort of distinction hardly seems to matter. The fact is that both are expected to perform at about the same level, with much the

same degree of technological expertise, and in consequence of this each now shares or soon will share many of the same professional aspirations.

Let us examine what is occurring. We have started to embark upon complex and costly programs to train various kinds of physician’s assistants who are to perform various functions at a fairly high level of technological sophistication. The navy “corpsman” or the army “medic” has been the ideological model. He is to serve as the physician’s helper, either as his aide in the office, clinic or hospital, or as his agent in isolated or remote areas. Certain specialties, notably pediatrics and orthopedics, have now begun to develop their own specialized physician’s assistants. Internal medicine is studying the possibilities. But while all this is going on, there are already elaborate programs, some more formal than others, to train nurses to perform many specialized functions which are quite difficult to differentiate from the kinds of functions proposed for physician’s assistants. There are nurse anesthetists, surgical nurses, psychiatric nurses, public health nurses, office nurses, visiting nurses, and specially trained nurses who serve in intensive care units, coronary care units and post-operative recovery rooms, and there are nurse administrators of many kinds.

If one reflects upon this, he must sense that for some time we have been developing a health professional with a higher level of professional sophistication than we have had in the past. So far professionals of this order have been mostly women who have evolved from nursing backgrounds. But now a parallel development is occurring with the “physician’s assistant” programs which will prepare mostly men for similar if not the identical roles. Perhaps what is really happening is that a new category of health professional is arriving upon the scene, one which will embrace a variety of trusted operational roles in the delivery of medical care and health care services, and whose membership in due time will reject the role of nurse, and also the image of assistant, in favor of a new and well-earned professional status. This new category of health professionals has yet to acquire a generic name, but those it encompasses are already well started in the performance of their categorical functions. Physicians should look forward to further developments which seem certain to be in the interests of better patient care, and from the standpoint of the community, better health care.

CASE REPORTS

Isotope Evaluation of Splenic Size in Hereditary Spherocytosis

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THE EXAMINATION OF THE spleen by physical methods has long been recognized as difficult, dividing examiners into feelers and nonfeelers, both of whom at times doubt the validity of the others' findings. While a palpable or percussed enlarged spleen can frequently be verified, determining that the organ is not enlarged may be more difficult. X-ray examination without the use of contrast media and selective angiography has also proved to be of limited value.

More recently, the spleen has been studied with various radioactive substances, permitting nearly 100 percent visualization of the organ as well as evaluation of its size and function. The materials used are generally prepared as colloids which are phagocytized by the reticuloendothelial cell. Less frequently, isotope-labeled denatured or injured red blood cells are used. The availability of shorter-lived isotopes such as ^{99m}Tc technetium (^{99}Tc) and ^{113}In indium (^{113}In) for colloid preparation have made the more tedious method of red cell tagging less popular.^{1,2} Even though the reticuloendothelial system as a whole is visualized with these newer isotopes, it is possible to give millicurie amounts of radioactive

material so their relative lack of specificity for the spleen (approximately 10 percent of the dose in normal persons) does not hinder good visualization, provided proper views are obtained.

The availability of ^{99m}Tc sulfur colloid, the low patient radiation dose and the ease of use have made it the most popular material for splenic visualization at the present time. It is important to recognize, however, that other preparations (such as colloidal indium and microaggregates of ^{131}I albumin) give satisfactory results.

Two cases of hereditary spherocytosis are presented to illustrate the value of splenic visualization when other methods of splenic evaluation failed or were of questionable value.

Procedure

Each patient was given 1.5 to 2.0 millicurie of ^{99m}Tc sulfur colloid intravenously 10 minutes before visualization. No patient preparation was required before the studies were carried out. The Pho Gamma III scintillation camera with the 4,000 hole low energy parallel collimator, detecting the 140 kev gamma rays of ^{99m}Tc , was used to visualize the liver and spleen. The time required to collect 200,000 counts on an anterior hepatic view was determined. Right lateral, left anterior oblique, left lateral and posterior views were then obtained, using the preset time. The images were registered on Polaroid® film to allow comparison of both liver size and uptake with that of the spleen. ^{57}Co cobalt point sources were placed 10 cm apart on the camera face to provide a Polaroid image which could be later used as a size reference for evaluation of subsequent organ images. Markers previously placed on the xiphoid and costal margin further aided in the interpretation. Each view required approximately 2 minutes and the entire study 10 to 15 minutes.

Reports of Cases

Case 1. A 51-year-old white man was admitted for evaluation of hypertension and a hemolytic process. The latter presumptive diagnosis was

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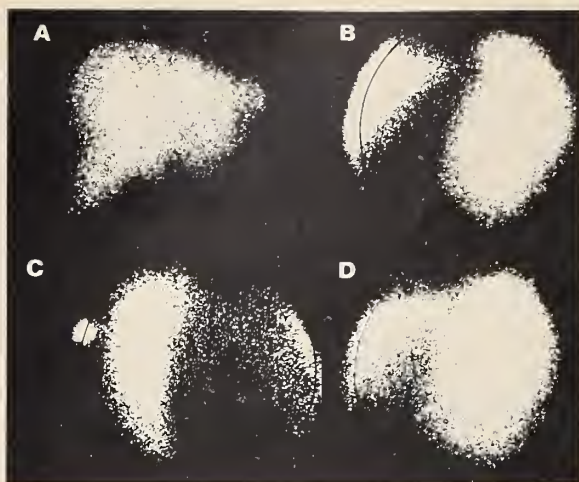


Figure 1 (Case 1). ^{99m}Tc sulfur colloid scintiphotos of spleen and liver with ^{57}Co markers on the xiphoid and costal margin.
A. Anterior Liver B. Left Ant. Oblique Spleen
C. Posterior Spleen D. Left Lateral Spleen

based on blood smears which showed increased reticulocytes and frequent spherocytes. One x-ray report suggested the presence of splenomegaly but this was not confirmed by physical examination. The initial blood pressure was 160/92 mm of mercury and the patient's eye grounds showed mild hypertensive changes. There was no adenopathy. The spleen could not be felt by a number of examiners who palpated the area, even though they knew it to be enlarged.

Laboratory studies included a relatively normal hemogram except for the presence of many spherocytes and an increase in reticulocytes. Osmotic fragility studies were consistent with hereditary spherocytosis both before and after incubation in normal saline solution for 24 hours. Coombs test results were repeatedly negative; no abnormal proteins were noted. A red cell survival study performed with ^{51}Cr labeled red blood cells revealed shortened red cell life with a half life of 15 days (normal 25 to 35 days). An attempt to determine a spleen-liver ratio was unsuccessful. Spleen and liver scintiphotos using ^{99m}Tc sulfur colloid revealed the spleen to be approximately three or four times normal size (Figure 1). The basis of size estimation was visual evaluation alone. Splenectomy was recommended and performed. At operation the spleen was found to weigh 600 grams, or four times the normal weight.

Case 2. A 63-year-old white man was admitted with chief complaint of "cancer of the blood."



Figure 2 (Case 2). ^{99m}Tc sulfur colloid scintiphotos of spleen and liver with ^{57}Co markers on the xiphoid and costal margin.
A. Anterior Liver B. Left Ant. Oblique Spleen
C. Posterior Spleen D. Left Lateral Spleen

He gave a history of episodes of painless jaundice and recent loss of energy. A brother also had episodes of jaundice and a son and sister had been treated for "low blood." The patient was pale and sallow without clinical icterus. The admitting intern recorded a palpable spleen, a finding which was not confirmed by other examiners. The packed red cell volume was 35 percent; reticulocyte count 9.2 percent; Coombs tests negative and bilirubin 2.15 mg per 100 ml with 2.13 mg indirect. Liver function studies and gall bladder x-rays were within normal limits. The bone marrow was hyperplastic with decreased iron stores. Spherocytes were present. Osmotic fragility tests became positive after incubation in saline solution for 24 hours. A spleen-liver ratio done with ^{51}Cr labeled red cells was 3:1 and the erythrocyte survival half life was 17 days. X-ray examination did not show splenic enlargement. The spleen was approximately three times enlarged both by ^{99m}Tc sulfur colloid scanning and scintigraphy (Figure 2). There also appeared to be irregular hepatic uptake consistent with cirrhosis.

Splenectomy was advised. The removed spleen weighed 455 grams and measured 16 x 17 cm. Liver biopsy was not done but the organ was grossly normal.

Discussion

These two cases of moderate splenomegaly, difficult to discern by physical examination, are

representative of many situations where evaluation of the anatomy of the spleen is of importance in either diagnosis or treatment. Hereditary spherocytosis is usually satisfactorily controlled by splenectomy. Preoperative visualization of the spleen aids in confirming the diagnosis as well as in recognizing accessory spleens. Figures 1 and 2 show the clarity with which the spleens in these two cases were visualized. Multiple views are important to determine the size and position of the spleen. The left anterior oblique view most frequently visualizes the organ best.

The finding of splenomegaly at operation in these two patients with hereditary spherocytosis confirmed the value of this procedure as an aid in determining spleen size. Though it appears that the spleens were large enough to be found on physical examination alone, the patient's body habitus and the posterior position of the organ precluded this in these patients, suggesting the possibility that spleens of lesser size may be missed even more frequently. The ease and safety of the procedure further enhances the desirability of scintiphotography as a diagnostic tool. For less enlarged spleens there are methods of predicting volume with reasonable accuracy although in obviously enlarged organs, such as these, visual examination alone is usually sufficient.

Summary

In two cases of hereditary spherocytosis splenomegaly was not discovered by physical or x-ray examination. Both patients were studied by scintiphotography, using ^{99m}Tc sulfur colloid as the spleen labeling agent. The finding of an enlarged spleen by this method in both patients was corroborated at the time of operation. These findings illustrate the value of this procedure.

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Myelography with Sodium Diatrizoate (Hypaque®)

Report of a Case of Inadvertent Use Complicated by Acute Renal Failure

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ALTHOUGH WATER-SOLUBLE contrast agents have been used for myelography, the pronounced toxicity and special precautions have brought these agents into disfavor in this country. Therefore for myelography or other procedures, direct intrathecal introduction of water-soluble contrast media is an infrequent occurrence.¹⁻⁸ However, in one previously reported case, a myelogram was performed with such an agent, and acute renal failure was a complication that followed. This paper reports another case of acute renal failure following myelogram performed with sodium diatrizoate. (Hypaque®)

Report of a Case

A 25-year-old Caucasian man was admitted to a hospital for evaluation of back pain after five days of lumbar traction. A myelogram was performed. Spinal fluid examination before the myelogram was normal. Fifteen milliliters of spinal fluid was removed and 5.0 ml of sodium diatrizoate was instilled into the subarachnoid space. This caused immediate but mild lower back and coccygeal pain radiating posteriorly into both thighs. After five minutes the pain spontaneously subsided. Another 3.0 ml of the same contrast medium were injected, again producing pain. The procedure was discontinued and the pain again quickly subsided. Two hours after the initial injection, severe pain recurred, associated with burning, paresthesias and pronounced spasm of the rectal, gluteal and anterior thigh muscles.

Over the next half hour the patient received 2.0 ml of dexamethasone, 1.0 ml of methapyrilene compound, 50 mg of meperidine hydrochloride, 25 mg of promazine hydrochloride, and 8.0 mg of morphine sulfate, all intramuscularly. This gave no relief of the severe muscle spasms, which had spread to involve the entire lower half of the

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body. Tonic-clonic seizure activity was observed and 15 gm of sodium amytal was given. Blood pressure fell from 125/80 to 90/30 mm of mercury. During the next hour, an additional 7.5 grams of sodium amytal, 2.0 ml of levarterenol bitartrate, 30 ml of dexamethasone, 50 mg of hydrocortisone sodium succinate, and 0.75 mg of digoxin were administered intravenously, and the patient was transferred to Tripler General Hospital.

On arrival, approximately five hours after the myelogram, he was semicomatose, responding only to painful stimuli. Blood pressure was 120/70 mm of mercury, pulse 80 per minute and temperature 37.5°C (100°F). Pupils were equal and reactive, and corneal and pharyngeal reflexes were present. Muscle tone was flaccid, but intermittently there was diffuse extensor spasm lasting 30 seconds. Deep tendon reflexes were symmetrical and hyperactive, and there were bilateral extensor plantar reflexes. The remainder of the physical examination was normal.

Leukocytes numbered 20,600 per cmm, with 93 percent neutrophils and 7 percent lymphocytes. The hematocrit was 42 percent and hemoglobin content was 14 grams per 100 ml of blood. Urinalysis showed many red blood cells but an otherwise normal sediment, and there was no proteinuria. Blood urea nitrogen (BUN) was 23 mg per 100 ml, serum glutamic oxaloacetic transaminase (SGOT) 1533 International units, and barbiturate level 3.0 mg per 100 ml. Serum haptoglobins were decidedly decreased (25 mg per 100 ml). The remainder of routine laboratory studies were normal.

Hospital course. The bladder was catheterized and 600 ml of dark, muddy brown urine were obtained. Spectrographic analysis showed the dark pigment in the urine to be methemoglobin. Lumbar puncture was done and the fluid was normal with a protein content of 24 mg per 100 ml. An electroencephalogram showed diffuse three-cycle-per-second waves. The patient became severely oliguric and was unresponsive to mannitol or furosemide. His semicomatose state was attributed to barbiturate intoxication and possible encephalopathy secondary to the sodium diatrizoate. Pulse rate and blood pressure remained normal. He did not require intubation nor vasopressor therapy. There was no further seizure activity. Twelve hours after admission he was responsive to verbal command and could

move all extremities. At the end of 24 hours he was fully alert and oriented but complained of low back pain radiating in a sciatic distribution and weakness of both legs. Progressive azotemia necessitated hemodialysis on four occasions over the next 14 days. Later he entered a diuretic phase and had complete recovery of renal function. Renal biopsy was not performed. Creatinine clearance at discharge was 140 ml per minute.

Because of persistent pain and weakness, a neurosurgical evaluation and electromyographic studies were obtained. These revealed no evidence of arachnoiditis, anterior horn cell disease or peripheral neuropathy. Symptoms were felt to be secondary to neuralgia caused by sodium diatrizoate. After six weeks in hospitalization the patient still complained of mild back pain and posterior numbness of both thighs, but otherwise he had completely recovered.

Discussion

Several investigators^{2,9-11} have demonstrated the pronounced toxicity of intrathecal sodium diatrizoate in animals, and its toxicity following similar injection in man is clearly stated in detailed literature accompanying the drug.

Of the 16 previously reported cases of accidental intrathecal administration of water-soluble contrast media, six were complications of discography, one was incident to a myelogram, one was from injection into a myelocoele, and the remainder were complications of cerebral (seven cases) or translumbar (one case) angiograms. Four of the 16 patients died; 12 had complete recovery. The contrast media used were sodium diatrizoate (11 cases), iodopyracet (three cases), and Urografin® (two cases). The volume of material administered ranged from 2 to 40 ml. It is not clear from the available data whether the type of contrast medium used related to the severity of the reaction. Symptoms do not seem to be entirely dose-related since there were two fatalities at small doses (6 and 8 ml) and two at large doses (30 and 40 ml). With the exception of the myelocoele, the other three fatalities occurred in instances of cerebral vessel angiography where the contrast medium entered the high cervical or cisternal subarachnoid space. Thus, it appears that the proximity of the contrast medium to the intracranial subarachnoid space is as critical a factor in determining the severity and outcome as the dose of medium in-

jected. Similar observations were made by Praestholm and Lester¹² and this concept is also suggested in animal work by Hoppe and Archer⁹ and Campbell et al.¹⁰

Clinically, a typical sequence is seen. Initially there is mild to severe, usually transient, pain in the area of injection. This is then followed frequently, but not always, by an asymptomatic period lasting from 30 minutes to two hours. Extreme pain, severe extensor spasms, hyperirritability and, in severe cases, convulsions may then develop. Both hypertension and hypotension have been initially noted. In severe cases, shock and apnea may ensue. In the reported fatal cases, death occurred within 2 to 4 hours; in the non-fatal cases, recovery was complete within 2 to 5 days.

Because of the potential seriousness of such accidents, treatment should be administered as soon as it is realized that water-soluble contrast medium has entered the subarachnoid space. Unfortunately, the treatment of this complication is not clearly established. Suggestions have included: elevating the head and shoulders to allow gravity flow toward the lumbar area;^{2,5} lumbar puncture with removal of cerebro-spinal fluid, followed by cisternal puncture and irrigation of the subarachnoid space;⁵ and sedation, usually in high doses, to control seizure activity. Corticosteroids, either systemically or intrathecally, have also been used. Other than basic supportive treatment, however, there is no evidence of the effectiveness of any of these means of treatment.

The pathogenesis of the central nervous system manifestations of this unusual problem is not known. Direct irritation of spinal cord has been postulated by most observers; however, Fundquist and Obel¹¹ expressed belief that the injurious effects may result from the hypertonicity of the contrast medium, rather than from a specific toxic action. The few post-mortem studies reported^{2,8} have demonstrated no significant or specific central nervous system changes.

The cause of the acute renal failure in both the present case, as in that reported by Turner et al,¹ remains unclear. In both cases there was evidence of probable intravascular hemolysis and in both cases dark, muddy brown urine was noted. The urinary pigment was not identified by Turner et al, but in the case here reported it was found to be methemoglobin. We have no data to

indicate whether the methemoglobin was filtered through the glomerular membrane or formed in the urine, although the decreased plasma haptoglobin levels suggest that there was intravascular hemolysis. It has been shown in experimental animals that methemoglobin is a more potent chemical inducer of acute renal failure than mercury.¹³ The patient in the present case also had pronounced hypotension and received treatment with a potent vasoconstrictor, which may well have contributed to the acute renal failure.

Summary

A 25-year-old Caucasian man was admitted to hospital in semicomatose condition five hours after a myelogram had been administered with sodium diatrizoate, a water-soluble contrast agent considered decidedly toxic and therefore not held in favor for such use in the United States. The patient had neuralgia, also caused apparently by the sodium diatrizoate, and acute renal failure which necessitated hemodialysis on four occasions in a period of 14 days. After six weeks in hospital he still complained of mild back pain and numbness in both thighs posteriorly, but was otherwise completely recovered. Although the acute renal failure is not etiologically clear, the potent vasoconstrictor which the patient had received before arrival at the hospital may have well contributed to the condition.

TRADE AND GENERIC NAMES OF DRUGS

Hypaque® sodium diatrizoate

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The Doctor and Sex Education

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THERE IS A DELUSION prevalent in our society that sex education given to children by their parents is adequate. More, it appears to be believed in some quarters that preventing teachers from giving sex education will somehow protect children from prurient stimulation. Sex education, always controversial, has now become a passionately argued issue. The opposing forces charge one another with everything from stupidity to treason. The concerns identified by foes of sex education range through fear of "communist enslavement of our country" to at least "undermining the moral fabric of our society." Such terrors have led to the use of tactics like distortion, outright prevarication and personal intimidation to prevent sex education. Physicians are to be found on all sides of a question that has many facets. They are advisors, proponents and opponents. Since their efforts to help patients and other laymen are often hampered by their lack of understanding of what generates the savagery of the antagonists, a dispassionate examination of sex education is advisable if they are to contribute constructively to solving the problem.

From 71 to 95 percent of parents in communities which were polled approve of sex education programs in the schools.^{1,2} From 5 to 29 percent disapprove even when attendance by their children is voluntary, not compulsory. To understand these numbers it is necessary to know what is

being approved or disapproved, and why. One must examine what the sex education programs are, and consider what they ought to be. Eventually, in evaluating indications and contraindications for public school sex education, it will be necessary to clarify the goals of such programs and the evidence of need for them.

According to the proponents of public school sex education our society is suffering from effects of sexual ignorance.³ The rising rates of venereal disease and illegitimate pregnancies among our adolescent population are blamed on "sex." For some proponents sex education really means indoctrinating children to avoid sex before marriage. Advocates of this view also recognize that education about venereal infection may be helpful in avoiding disease, although prevention of any sex rather than "safe" sex is their goal. Paradoxically, some opponents of sex education also wish to indoctrinate children with a belief in premarital chastity. Sex is to be avoided not only because it "causes" venereal disease and illegitimacy, but because premarital intercourse is "morally wrong" and may weaken our society by eroding the moral base upon which it rests. Some weary and thought-worn parents suspect that sexual experiences, including coitus, will occur before marriage, as they always have, despite the fearful consequences of venereal disease and pregnancy. Viewing the consequences seriously, such parents want their children to know about contraception and hygienic sexual practice even if they deplore the risks their children take in having premarital coitus.

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It is ironic that some people *want* sex education in order to diminish premarital intercourse, while others *do not want* sex education in order to diminish premarital intercourse. The latter believe, obviously, that children who learn about human sexuality, and who learn how to avoid the risks of disease or unwanted pregnancy, will copulate in greater numbers than those who remain ignorant of sex or fearful of its consequences.

There is yet another faction, much less vocal and less certain than the previous two, which shares the concern over the dangers to our society of rising venereal disease and illegitimacy, as well as increasing divorce rates, over-population, and unavoidable human suffering. Those who advocate broader sex education for those reasons believe that our traditional and repressive attitudes toward sex have led to tragic ignorance. The effective result has been that premarital sexual experience continues, as it always has in human existence, but feelings of guilt and fear haunt the sexual lives of too many. Those people who view sex as "bad" tend to avoid knowledge of sexual practices, contraception and infection, though they do not necessarily avoid sexual experience. Venereal disease, while deplorable, is often curable. Unwanted pregnancies, while tragic, are often temporary concerns, being resolved by the estimated one million criminal abortions obtained by United States women annually, or in many instances by adoption. Forced marriages and raising unwanted children produce more persistent misery.

Perhaps least recognized of all the consequences of sexual ignorance is the needless suffering of sexually-dissatisfied and maladjusted couples. Those who experience failures in their sexual lives are generally silent. They reveal themselves to their physicians or clergymen but rarely to anyone else. They feel ashamed, inadequate and cheated, because sex has been a source of pain, not pleasure. Couples quarrel, philander, and endure their unrewarding sexual relationships, too inhibited, too ignorant, and too guilty to correct their problems. They rarely die from it, but they suffer needlessly as a result of the inadequate and malignant sex education they have received.⁴

What is the evidence for these contentions? On what basis can one assume that sex education

or its absence contributes to immorality, illegitimacy, venereal disease, more divorce or increased human suffering? One would never know, from listening to the noise of the debate, that the debaters have such flimsy arguments.^{5,6,7} For example, any physician knows that venereal disease, although spread by coitus, is caused by viruses and bacteria, and treated with antibiotics. Those deploring premarital coitus blame it for increasing venereal disease and conveniently ignore the fact that the organisms causing it are becoming rapidly resistant to the drugs used to control them. They also overlook the effect of cultural attitudes that "sex is bad," which often leads to embarrassment in the infected person who avoids seeking necessary treatment.

Illegitimate pregnancies might be a reflection of a more permissive and accepting attitude toward sex. But we should realize that the increasing illegitimacy has been occurring among children reared and educated before the modern sex education programs were begun. The children having babies out of wedlock are mostly those who have not received public school sex education. What they have gotten has come from other sources, including their parents' homes, their churches and their peer groups as well as the mass media of communication.

Divorce rates are increasing and many factors have been implicated, including among them sexual incompatibility, adultery, a more accepting attitude toward divorce by the courts and society, as well as longer life spans for the spouses, urban living and emancipation of women. It is difficult to fix the major blame on sex education if the other causes contribute. It is ridiculous to blame sex education primarily, when the people divorcing were never exposed to the developing school programs that are now being opposed.

Some available evidence supports the claim that sexual maladjustment, impotence, frigidity, and general dissatisfaction with the sexual side of life are widespread.⁸ Surveys of practicing physicians suggest that most so-called "normal" and "healthy" people experience sexual problems, of greater or lesser severity, at various points in their lives. People who have conducted such surveys feel that attitudes toward sex which foster ignorance, inhibition and guilt contribute significantly to sexual maladjustments.^{4,8}

With some of the effects of sexual ignorance

identified, it might be possible to establish goals for a sex education program. It is desirable to strengthen society generally (rather than cause its downfall); illegitimate pregnancies, venereal disease and divorce are to be avoided; the sexual lives of human beings should be gratifying and fulfilling rather than miserable and disrupting; and unrealistic expectations of sex and attitudes of inhibition and guilt should be discouraged. To state it more simply, we should educate people to enjoy the benefits and satisfaction of sexuality and to avoid the misery and tragedy of it.

As in any form of education, the program is concerned in varying degrees with influencing *attitudes*, imparting *knowledge* and developing *skills*. There is no obligation for any school to approach this task in any particular way. Presumably, each community and school system, in consultation with parents and educators, decides what its program should be. As a result, sex education is quite variable from school to school and from district to district, depending upon what the goals are, what is taught, who teaches and how effectively. The factual knowledge may be as broad as the nature of interpersonal relationships within a family and as specific as the anatomy and physiology of human sexual response. The skills may vary from an enhanced ability to speak with parents about sexual concerns to the use of contraceptives. The attitudes, depending on the community's wishes, may vary from "thou shalt not" under any circumstances, to a more open evaluation of whether or not one should engage in sexual relationships and why.

The backlash of opposition to public sex education began in the summer of 1968, although programs of education in "Family Life" and "Human Sexuality" had been around for years. SEICUS (the Sex Education and Information Council of the United States) has been in existence for about six years and its avowed purpose is to "promote healthy, responsible relationships between male and female in all aspects of human behavior, not limited to the 'sex act'." More extensive school sex education programs began to spring up at about the time SEICUS was formed, both events being the *result* of increasing openness about human sexuality in our society and increasing awareness, therefore, of the amount of sexual maladjustment and human misery attributable to sexual

ignorance. The first vocal opposition was from the Christian Crusade, a fundamentalist, right-wing organization headed by the Reverend Billy James Hargis. According to the *New York Times* of 14 September, 1969, it was not until six months later that the John Birch Society saw sex education programs as a Communist plot. Robert Welch, of the Birch Society, writing in the January 1969 edition of *J.B.S. Bulletin*, called for a nationwide campaign to oppose sex education. The call seems to have been extremely effective. The coalition of fundamentalist religious groups and arch-conservative political groups has decided that sex education generally and SEICUS particularly are immoral, anti-religious and Communist-inspired plots to ruin the children, the country and the world.⁹ Enough people have been frightened by these assertions to cripple many sex education programs and prevent others. The motivations and techniques of the opponents of sex education deserve scrutiny.

Some observers believe the Birch Society's opposition to sex education is really directed against public education by the state generally, because of the fear that the state is vulnerable to Communist control. Sex education, an emotion-laden issue, lends itself nicely to exploitation by the John Birch Society and draws together, as allies, elements that are not otherwise in agreement with the means and ends of the extreme right wing. Even if there is some hypocrisy among them, most opponents of public school sex education are passionately sincere. The literature they disseminate states that school programs lack morality because there is no religious frame of reference upon which to base premarital chastity, and presumably marital fidelity.^{10,11,12} They claim that sex education is harmful to children because it stimulates them sexually, leading to psychiatric problems. They cite Freud's description of a "latency" period in the personality development of children, from roughly age 5 to puberty, and suggest that exposure to sexual information during that age is unnatural, harmful and psychiatrically contraindicated. Fundamental religion and Sigmund Freud may seem strange bedfellows, indeed, but there are stranger and more disturbing aspects of the attack on sex education.

Most people who are frightened or threatened

by "sex" can accept that morality and moral behavior may exist when there is not a traditional or fundamentalist religious sanction for it. Even if we had no system of laws to control sexual behavior, there are many powerful arguments, based on secular considerations alone, for and against sexual experiences in childhood. Regarding Freud's "latency" period, there is extensive controversy among modern psychiatrists as to whether such a thing even exists. Although children may appear to be uninvolved in sexual preoccupation, appearances are deceiving. Anyone willing to talk with or observe "latency" age children quickly realizes that they are as curious and concerned about sex as human beings of any age. With the barrage of sexual stimulation overwhelming our society, it is absurd to think that elementary school children can be or should be protected from "sexual" information in order to prevent mental illness. There is more evidence that "smog" or chewing gum causes mental illness than there is for an awareness of sexuality being responsible.¹³ Distorted, incorrect and frightening information may possibly be harmful, but that is more readily available outside the classroom than in it.

Other objections from the anti-sex forces concern such basic issues as whether instruction in methods of sexual behavior can be seen by children as encouragement to practice. A closely related issue is whether education given by the schools will conflict with or undermine education given at home. Implicit in such questions is fear and ignorance of public school sex education programs. Although they vary, the most liberal programs deal directly with whether or not children should experiment sexually. A consideration of parental values and standards is absolutely necessary to any sensible or healthy choice of behavior. If parents have done a good job of indoctrinating their values, and if they provide a strong justification for them on religious and other grounds, the child will not be confused or corrupted by an examination of the issues. People who have been raised to think of human sexuality as dangerous, unpredictable and destructive, of course fear it. Aware, nevertheless of their own sexual feelings striving for expression and controlled only with some effort, people assume that anyone without their strongly indoctrinated guilt and inhibition would do what they *want* to do. They fail to appreciate that sexual repression

rather than too much freedom is the source of their conflict. They treat the malady with more of what causes it, making it worse, not better. Yet, they have been raised to believe so strongly in the essential evil of human sexuality that it is almost impossible for them to consider that sexuality can be controllable, comfortable and constructive for them or their children.

The case for the opposition comprises several other points. Sex education will not cure social ills and may be illegal. Granted. Public sex education programs are SEICUS-influenced and SEICUS is accused of a Communist taint. The evidence consists of the repeated mention of recently deceased Isadore Rubin, a former member of the Board of SEICUS and editor of the magazine *Sexology* which too often had lurid covers or lurid titles for articles. Rubin was once called before the House Committee on un-American Affairs and refused to state whether he was a Communist. International Business Machines, one of the leading American corporations and a contractor for many top secret defense projects, has been accused of being Communist-influenced because one of its subsidiaries, SRA, was in the business of preparing sex education materials.¹⁴ The irony of pandering to the fear of Communism is that Russia has been criticized by its own population for suppressing sex education programs, thus aligning it solidly beside the John Birch Society and the Christian Crusade.^{15,16}

The most appalling aspect of the backlash is not its ends but its means. Statements made by their propagandists are often misleading because they are taken out of context. According to the *New York Times*,¹⁷ there have been numerous claims that sex educators or sex education have been responsible for several offensive incidents. In each case where the stories were investigated it was found that the claims were untrue or distorted. Obviously any extensive educational program will fail at times, or individuals within it will, but the "scare" tales are believed by those who are not aware of the dishonesty. Another common ploy is to cite an "authority" as a method of influencing belief. The credentials and expertise of "authorities" may be unreliable, but gullible and frightened people are prone to accept the statements made by almost anyone so labeled. Since so many people are guilty and anxious

about their sexuality, it is easy to intimidate them into silence by suggesting that anyone who opposes a given point of view is immoral. The fear of being ostracized or ridiculed is reason enough to behave in conformity with the ideas of the accuser. When all else fails, the Bible is quoted as authority, although many people have noted that verses and passages can be found in it to appear to support the legitimacy of almost any belief.

Before concluding that sex education is good or bad, it would be useful to address the problems of evaluation. If one accepts the goals of a sex education program to be knowledge, skills and attitudes leading to increased happiness, sexual adjustment and satisfaction, and less venereal disease, illegitimacy and divorce, it will be an *impossible* task to evaluate the success or failure of the effort. This applies equally to the problems of evaluating the effects of no public school sex education. One can ask students, before and after a course, to demonstrate their knowledge, but it is extremely hard to evaluate the benefits of that knowledge when it may be applied ten years later. Attitudes are much harder to measure, and sexual skills, in our present social climate, are, practically speaking, impossible to measure.¹⁸ There are so many influences contributing to happiness or dissatisfaction, unwanted pregnancy or divorce that only a massive study of hundreds of thousands of people over decades, costing many unavailable millions of dollars could hope to clarify the effects of such variables as public school sex education. However, the arguments *pro* and *con* are based not on logic but emotion, not fact but impression, and all too often on lies.

Recently we conducted a survey among those people who opposed sex education in the schools to learn more about them and the reasons for their opposition. The people surveyed were from Southern California and notable for their publicly expressed opinions on sex education. Twenty-four were contacted for the survey and five would not take part. Of the remaining 19, 15 were opposed to sex education in public schools. These 15 were interviewed from 30 to 60 minutes. While some specific questions were asked, the interviews were kept as open-ended as possible so that the interviewees could respond to those parts of public sex education about which they felt most strongly.

Results

Of the 15 people, 13 were men and two were women. The age range was from 35 to 64, and eight of them had an annual income of more than \$20,000. All of them were married and the number of children ranged from none to five. Five were Catholics, nine were Protestants, and one belonged to no formal religion. All had at least finished high school and 12 had graduated from college. Six of them were professional people, two were housewives, and the remainder were either in business or schools. They were an intelligent, well educated group. Most of them (eight) had learned of sex between ages 7 and 13 or during the "latency" age period. Of the 15, only six had received their knowledge of sex at home. Only four recalled that their parents took direct responsibility for providing sex education. In answer to the question, "What did you learn?" four answered, "What everyone else learned"; one said, "About menstruation"; four answered "Simple reproduction"; and three gave no clear answer.

Because people's opinions about public school sex education vary with their concept of what is being taught, we asked each individual what he thought was included in public sex education. Their ideas ranged anywhere from simplified reproductive physiology and anatomy to morals, masturbation, and sex techniques. Ideas about the age at which instruction began ranged from 5 years old to 17 years old.

All the 15 people felt that the home was the correct place for sex education. In educating their own children, their approach varied from beginning at age three with an informal presentation and becoming progressively sophisticated from there, to beginning at age 13 and responding only when asked by their children.

The concerns about public sex education that were voiced during the interviews can be grouped into four broad categories: (1) concern about the lack of teaching of morals, (2) concern about the effect of the school teachings on the home life and the parents, (3) concern about the children, and (4) concern about the teachers and the approach and content of the classes. By far the most often expressed criticism (by ten of the 15) was of lack of the teaching of morals—that is, that no standards of conduct were set for the

children. Concern about the effect on the home and parents took the form of specific complaints that there was no regard for parents' feelings in the course planning and that the material learned was in direct conflict with that taught at home. In addition, general complaints that "teaching sex tends to destroy the home," and that "the generation gap is widened by such courses" were voiced.

In expressing their concern about the children, arguments were put forward that "the kids cannot handle this material," that "the material being taught is sensual and it (sexually) stimulates them," that "there is no resolution of any conflict presented so the kids are mixed up," that "the classes are too emotional and embarrassing," that the children do not need the information, and that teaching about sex destroys the capacity to love, thereby leading to promiscuity.

In the final category—that of concern about the teachers and the approach and content of the classes—the interviewees stated that the teachers are unable to judge at what age each individual child is ready for sex education. Some felt that the teachers were poorly equipped, suggesting that a few teachers have sexual hang-ups themselves. It was also felt that teachers impart their own philosophy, whether consciously or unconsciously, to the children. Specific criticism about the classes were that they should be voluntary, that they teach that masturbation is all right, that giving these classes will not decrease the illegitimate birth rate, the venereal disease rate nor the divorce rate, and that the approach is a negative one and "too much like sensitivity training." The opinion was expressed that the classes were too complete, that they should instead be incorporated into a health course and that the sexes should be separated.

A topic closely related to the public school sex education controversy is that of the role of the Sex Information and Educational Council of the United States. Twelve of the people interviewed were completely opposed to SIECUS. When asked about the reasons for their opposition, criticisms of the people involved in it were expressed. The criticisms were (1) that the people in it are immoral, (2) that they are (politically) liberal, (3) that some of them are not medical doctors, (4) that they are warped or strange, (5) that the people are too closely linked to *Sexology Magazine*, (6) that they encourage promiscuity, (7)

that they believe sex is to enjoy, (8) that they are agents of change, (9) that they are Communists, and finally (10) that they are anti-religious.

Discussion

Who should teach? Those opposed to public school programs insist that parents should have the responsibility for educating their own children as they see fit. They also say that teachers who instruct sex education courses are rarely qualified by virtue of special training or ability. If the teachers are not trained, and lack knowledge, teaching skills, or appropriate attitudes (and this is too often true), then there is little basis for arguing in favor of school programs. Besides it is cheaper, easier and more individualized to the needs of the child for his parents to teach him. But from experience it appears that parents rarely provide adequate sex education. Parents, like teachers, are too often ignorant, guilty, inhibited or unaware of their attitudes or the reasons for them. The alternatives are discouraging. We can educate the parents and thus qualify them to educate their children. This is unlikely and impractical, although desirable. We can educate the teachers after careful selection, and this is occasionally done. We could also decide not to have sex education classes in schools. Unfortunately, the choice is not one between school sex education and sex education at home. The choice is between thoughtful, planned, correct sex education at school, and distorted, inadequate, frightening, inhibiting and prurient sex education obtained in the streets, from the mass media and from the home.

Summary

The evidence suggests that people opposed to public school sex education prefer that parents provide sex education, despite indications that parents do not do an adequate job. The opposition is fearful, gullible, and misinformed. Their sincerity is unquestionable, but their facts are false. They properly identify the need for specific goals, community and parental voice in establishing goals, and training teachers, but their action is to prevent the educational program and, therefore, to perpetuate rather than correct the deficiencies.

Physicians must be aware of the complicated issues in order to act constructively.

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The Pacific Southwest Regional Medical Library Service

NELSON J. GILMAN, *Los Angeles*

IN THE SERIES of massive federal efforts to improve all facets of the delivery of health care, some funds were allocated for the improvement of medical and health science libraries—their collections, their service, their support.

Medical and scientific literature now is available to all doctors, dentists, nurses, pharmacists, and allied health professionals for the asking. The asking may be done through a local hospital library, or a health science library of a professional school, a college, university or medical center. The resources of the nearest local library are used first and the larger medical library of the area next in a chain or network ending with the National Library of Medicine. The Pacific Southwest Regional Medical Library Service (PSRMLS) is part of the nationwide Biomedical Communications Network sponsored by the National Library of Medicine (NLM) and functions as an intermediate link between NLM and local health science libraries in Arizona, California, Hawaii and Nevada. Located at the UCLA Biomedical Library, PSRMLS is one of 11 regional medical library services which strive to make health science information optimally available to health professionals. It serves health professionals in the four states by supplementing already available health science library service.

PSRMLS is advised by an 18-member commit-

tee which is broadly representative of the health science community. Twelve health professionals and six librarians serve on the committee.

To provide the health professional with the published information he needs for patient care or research or training, PSRMLS offers a variety of services as described in detail below.

Interlibrary Loan. Books and journal articles which are not available locally may be requested from PSRMLS through a health science library. PSRMLS lending is shared between the UCLA Biomedical Library and the library of the University of California, San Francisco. Requests from Northern California and Nevada are directed to UCSF Library; requests from Southern California, Arizona and Hawaii to the UCLA Biomedical Library. Requests which cannot be filled by PSRMLS are referred to other resource libraries. Interlibrary loan service includes provision of free photocopies of journal articles in lieu of the physical volumes.

Health professionals who do not have reasonable access to a health science library may request assistance through other libraries. If this approach is not feasible, such persons may request items directly from PSRMLS.

In the period 1 September 1969 through 30 April 1970, PSRMLS filled 22,400 interlibrary loan requests. Almost 70 percent of the items were sent from PSRMLS within one day after receipt of the request. Eighty-five percent of the items mailed were in the form of photocopies and they often went directly to the health professional's

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office for his immediate use. These copies are retained by the person receiving them; they need not be returned to PSRMLS. For example, a surgeon in Modesto, California, needs a specific article on congenital heart defects and finds that it is not available in his hospital library or in the larger medical libraries in his community. His librarian forwards the request to PSRMLS by mail, teletype or telegram. In emergencies a request may be made by telephone. The article is photocopied and sent by return mail to the surgeon's office. If for some reason the request cannot be filled, PSRMLS will notify the surgeon's librarian and forward the request by teletype-writer to the National Library of Medicine.

Medlars. MEDLARS (Medical Literature Analysis and Retrieval System) is computer-based system designed to achieve rapid bibliographic access to the world's biomedical journal information. One of the functions of MEDLARS is to provide bibliographies in response to persons asking for them. These bibliographies are produced on biomedical subjects for which printed indexes are not adequate sources. The search station at UCLA is part of PSRMLS. Search requests are accepted by interview, by submission of a standard request form, or by telephone. They may be submitted through a library or by individual health professionals. There is no charge for this service.

Reference and Bibliographic Services. Reference service is offered directly to the person asking for it, or through libraries by mail, twx, or telephone. It includes the following categories: (1) answers to factual questions where no interpretation of information is required, (2) short bibliographic searches on subjects not suitable for computer-based information systems, (3) bibliographies and information from MEDLARS and other specialized information centers, (4) identification of citations, (5) location of trans-

lations of foreign language material, (6) identification and referral service on medical films and videotapes, and (7) preparation of bibliographies and reading lists for use in continuing health professional education programs.

Consulting. At the request of a hospital administrator or librarian, PSRMLS will provide a consultant to advise in person or by mail on the planning, organizing, staffing or maintaining of a health sciences library. Sources of extramural support, preparation of grant requests, equipment and physical quarters, and recruiting sources are other areas in which the consultant may provide information.

The consultant visited 14 hospitals in the first eight months of PSRMLS' operations and assisted hospital administrators and librarians with library building plans, collection development, staffing and organization, and other problems.

Continuing Education. PSRMLS offers continuing education programs both for health science professionals and librarians. For the professional the services of the PSRMLS speakers' bureau are available. A variety of one-hour to two-hour continuing medical education programs could be presented by the PSRMLS staff. Topics include MEDLARS, current alerting services, basic abstracts and indexes, hospital library information services, and PSRMLS services.

One-day institutes directed toward personnel in charge of hospital libraries are given throughout the Pacific Southwest. Topics covered include book selection, reference services and the use of *Index Medicus*. Brief orientation sessions on PSRMLS services are also given to health science librarians.

Further information about PSRMLS services is available from the office of the Associate Director, PSRMLS, UCLA Biomedical Library, Center for the Health Sciences, Los Angeles, Ca. 90024.

Computerized Entry into Medical Care

Its Impact on Doctor-Patient Relationships

AVRAM YEDIDIA, M. A. BUNOW, M.P.H., AND MICHAEL S. MULDAVIN, M.P.H., Berkeley

■ A large proportion of cannery workers see a doctor only as a last resort, in time of crisis. The Cannery Workers Multiphasic Screening Program identified workers in need of physician evaluation, and referred each to a physician of his choice, for examination by appointment, while the worker was not acutely ill. In many instances the screening program generated the first encounters between patient and physician. It conducted a follow-up system for workers unaccustomed to methodical health care. The program financed pre-testing education of the persons to be tested, multiphasic testing, physician evaluation of abnormal findings, and the follow-up reminder system.

Each physician, in advance of the appointment for evaluation, was sent a computerized report calling attention to findings that exceeded limits considered normal. The report included a form facilitating the physician's report and billing. In counties having foundations for medical care, the foundations reviewed the form for adequacy of follow-up and appropriateness of charges.

The effort to bridge the gap between findings, diagnosis and therapy, for a population group newly introduced to modern medical care delivery, was made possible by the use of the computer as a tool for the attainment of specific, preanalyzed components of the total objective.

AS AN ULTRARAPID SORTER and reporter of data, the computer has become essential to the investigation, and even to the treatment, of certain diseases. But the concept of a computerized entry into medical care, by suggesting deperson-

alization, may appear to threaten the doctor-patient relationship, and through that to threaten the confidence that is a necessary part of therapy.

Four elements essential to a favorable entry into medical care may be discerned:

1. The patient must come to the physician early, before a health crisis arises, if the physician's skill is to have optimal effect.
2. The patient must if possible see the physi-

From the Health Testing Services, Inc., Berkeley.

Presented as part of the Special Conference, Multiphasic Screening: Help or Hindrance?, sponsored by the CMA Committee on Occupational Health, at the 100th Annual Session of the California Medical Association, Anaheim, March 15, 1971.

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cian by appointment so that there will be time to consider the case in a professional and concerned manner.

3. The visit should take place in the physician's private office, where his tools are at hand for adequate examination and for ordering of tests.

4. The relationship between patient and doctor must be stable enough, and the financial arrangements secure enough, that the doctor can provide adequate follow-up.

This kind of orderly entry into care probably characterizes a large portion of the practice of most private physicians. Up to the time of the intervention described here, the health care pattern of the workers involved stood in sharp contrast to this norm. About 30 percent of these workers are full-time employees of the California canning industry; the rest are seasonally employed and are among the lowest paid industrial workers in California. Many do not speak English. If they saw a doctor at all during their lives, they typically sought his help only when their condition was so desperate that his skill could not be effectively used. Many knew no physician. Many had no idea how to find one.

A factor not characteristic of all health programs for large population groups was stressed here: Those responsible for the Cannery Workers Multiphasic Testing Program were concerned that these persons should enter the health care system with privacy and dignity. They wanted the individual cannery worker's entry into medical care to have a positive educative value. They wanted to convince the workers that the health care available to them was desirable, attainable, and effective.

Because of the large number of workers involved, and the complexity and cost of the multiphasic testing system, the program had to be computerized. The question arose—as it must arise in relation to broadening segments of our country's total population in these days of population growth, mobility, and technology—whether the computer would help or hinder the attainment of the educative goal. The computer is, after all, the "personification" of the robot. Could it be used to help physicians to assure patients that they would not be treated like robots? Our experience appears to show that it could. The methods and results may prove relevant to a

variety of efforts to provide health care to our nation's growing, shifting, psychologically and sociologically changing population.

Cannery Workers Program

During the summers of 1967 and 1968, under the California Cannery Workers Program, persons employed in the canneries of this state (21,000 each summer) underwent multiphasic health testing by a prearranged mass program. Nearly 50 percent of these persons made their first entry into medical care as a direct result of this computerized routine. One index of the satisfaction with which the program was received is the increase, in the summer of 1970, in the number of participants to 22,620.

The health testing program consisted of a multiphasic examination designed and supervised by physicians, administered in a mobile unit consisting of three specially equipped trailers which visited the canning factories during the height of the fruit and vegetable packing season. Each step in the design and implementation of the program included careful attention to the needs and dignity of the individual tested. The program was designed to lay the foundation for achieving the four elements believed by its designers, as stated above, to be essential to the ideal entry into medical care:

1. *Entrance before a health crisis.* The program was focused on a specific population: the men and women working in the canning industry, with a characteristic pattern of seeking health care only for health crises. In order to identify those in need of physician evaluation, and to bring them to the attention of a doctor before a crisis arose, maximum participation was essential. If screening was merely made available to these workers, only those who already knew that they were sick would present themselves for testing. The easiest and least expensive way to assure maximum participation would have been to make testing compulsory, by joint decision of labor and management, as a condition of employment. But that would have violated the dignity of the individual, and would have stripped the program of its essential human worth. Since a fundamental objective of the designers was to preserve and restore the dignity of the individual, it was agreed that participation must be voluntary. A mass education program was projected.

To make maximum participation possible, testing was arranged at the plants during the canning season, when most of the workers could be present. The canning season is short: 3½ months; yard space is limited and the mobile unit occupied 100' x 100'. Workers had to be released from work at a crucial time which interfered with production schedules. During 1970, 90 days had to suffice for testing as many as 500 persons daily in 55 plants from Oroville in the north to Fullerton in the south. Management's commitment was strong enough, and cooperation of management and union was sufficient to solve these problems with remarkable smoothness.

In 1967, much concern was expressed about the probability of an adequate level of participation. In 1970 the problem was how to contain participation within available budget and time. Analysis pointed to specific factors as the reason for this response, from a population group not generally accustomed to planning for their health care: The program was planned jointly by those representing the Cannery Workers Union and the management of the plants involved. It was planned *with* rather than *for* the people who were to be examined. An educational program involving many persons on many levels in each plant (shop stewards, floor ladies, health committees, and others) was started well in advance of testing. It stressed the significance of the check-up to the tested individual, and the confidentiality of the test results: the report of the check-up was to be made available *only* to the examinees personal physician.

Testing was conducted in a friendly atmosphere, with a spirit of "Health Fair" and much cheerful give-and-take among participants and staff. Numerous written comments by cannery workers months after their testing experience confirmed this impression. No comment was made by any worker to the effect that the process was dehumanized, impersonal, or detrimental to human dignity. Each examined person was assigned a number, but no examinee was called by his number and during the testing probably none was aware that a number had been assigned. Upon completion of testing, each examinee was given a card on which his name and number were shown, with an explanation that if he were to make inquiry about his test results it would be helpful if both name and number were used.

2. *Physician appraisal by appointment.* To assure that the physician would have appropriate time for his appraisal of test results, two steps were required: (a) The basis for appointment with a physician was to be an abnormal result on multiphasic testing. It was therefore necessary to secure assurance of physicians' cooperation with the program. (b) It was assumed, and later corroborated, that many cannery workers would not have an established relationship with a physician. The linkage of such workers to specific physicians had to be facilitated.

To accomplish the first of these two steps, it was essential to establish high professional standards in testing, and to provide for flexibility in handling. Testing was to be conducted in areas served by 14 county medical societies with various attitudes and experience relating to screening. More than 1300 general practitioners and specialists were involved. In several of these counties, beginning in the late 1950's, Foundations for Medical Care had been established, through which prepaid health plans for employees had been administered; their experience led them to more ready acceptance of the program than could be expected of traditionally oriented societies.

In advance of testing, the program's consultant for professional liaison, Samuel R. Sherman, M.D., instituted joint discussions with representatives of these county medical societies. The representatives and the health testing program's professional staff together analyzed, modified and implemented the multiphasic panel. A physician's manual was developed listing the tests to be given, screening levels, and specifications for staff and equipment.¹

Procedures for assigning physicians to patients who had no physician, and for referral of patients to their own physicians for appraisal of abnormalities discovered on testing, were also developed at these joint meetings.^{1,2} The computerized Report of Multiphasic Health Check-Up for each examinee was sent to the personal physician designated by the examinee or assigned at time of testing. During the first testing period, only abnormal results were reported to the physician. Many of the physicians found that the information was valuable and should be incorporated into the patient's medical record. Their medical society committees recommended that the reports be sent for persons with normal

findings as well; beginning in 1968 this was done.

Examinees whose findings were normal received the following letter:

Dear Friend:

We are pleased to inform you that the results of your tests taken during the recent Health Check-Up were normal. We have sent a report on the results of your tests to the doctor shown on the enclosed card. This report will become a part of your medical record.

The Health Check-Up does not take the place of an examination by your physician, and we hope that you will continue to see your doctor for regular health care.

Sincerely,

Examinees with abnormal findings were urged to call their physicians and ask whether further evaluation was necessary. In 1970, for those who had also taken the test in 1968, the more recent report was accompanied by a report of the 1968 findings, providing the doctor with a comparison of results at two different times. Many physicians commented favorably on this improved tool for evaluation.

All of these reports were made possible by the computer. While computerized entry into medical care differed in structure from the familiar pattern, it effectively conserved a framework of orderliness, with consideration for the physician's professional demands and preferences, and for the personal relationship of the physician to his patient.

3. *Private office visit.* A simple computer print-out form, also sent to the physician for his use during the office visit for appraisal, was designed to facilitate his report to the health testing program of his estimate of the significance of the abnormal findings. A third form provided a convenient method for him to report diagnostic and consultative procedures performed or ordered, and constituted his bill for services rendered. Computerization greatly speeded the registering and analysis of these reports and the logistics of payment.

4. *Implementation of follow-up.* Full implementation of follow-up in the cannery workers' program evolved over several years. Until 1970, the collective bargaining agreement made funds available for the health testing program but not for follow-up. The industry has for years had an insurance plan covering certain health services, largely hospital-based with a few allowances for outpatient services. In 1967 and 1968 the trustees allocated funds for a public health nurse, social worker, and clerk to assist workers

whose test results indicated need for medical care and evaluation; but follow-up care was not covered. This raised the question whether the health testing examination might cause examinees to react against expense arising from the need for further health testing. This concern proved to be unfounded. The program has steadily emphasized the difference between the multiphasic test and a physician's physical examination, and workers understood that they must pay for their physician's services. Most of the workers met their obligations promptly. The burden placed on physicians by very poor families was solved by the collective bargaining agreement of 1969, which provided funds for payments for follow-up evaluation by physicians.

Adequacy of follow-up and appropriateness of charges were reviewed by the physicians' peers through a Follow-Up Evaluation Program implemented in 1970. It has consistently been the intent of the Cannery Workers health testing program, that wherever possible this review be first accomplished by organized medicine. Those medical societies with a Foundation for Medical Care were best equipped for these functions. The four Foundation counties with the largest number of cannery workers formed a committee of physicians and executives to meet with the program's administrators to develop procedures for follow-up evaluation. Guides for physicians seeing tested patients were drawn up on the basis of consultation with this committee and adopted by several other Foundation counties. In counties having no Foundation, the county medical societies reviewed the guides for physicians and volunteered to assist the health testing program in instances of inadequate follow-up or inappropriate charge. While non-Foundation counties do not routinely review or administer claims, they have settled minor difficulties informally by telephone, and granted more formal consideration to special problems. Even within the Foundation counties, arrangements have been tailored to the needs of the local medical community.

At the start of the Follow-Up Evaluation Program in 1970, physicians practicing in the involved counties had already had two years' experience with the testing program, through medical society representatives working with the program's professional consultants and staff, and through their own experience with some 10,000

patients referred each year to physicians by this program. They had recognized that the computerized entry of patients into medical care (1) gave important clinical information to the physician, (2) did not overburden the physician's office with the nonsick, (3) provided opportunity to implement preventive medicine—long desired, but difficult to accomplish within the constraints of daily practice, (4) gave the physician opportunity to provide inputs into the program directly or through his medical society, (5) did not encroach upon but in fact supported the physician's professional prerogatives, and (6) provided the physician with a set of useful tools (computer printouts) for the orderly recording and reporting of clinical information and for billing. The economic provisions for the medical care of the workers referred by the computerized testing program was as satisfactory as for the average patient at the start, and were reinforced in 1970 by financing for follow-up evaluation.

In addition to these direct advantages, the computerized method of entry into medical care has yielded a bank of information on the health status and needs of the large population served, which is of high potential value. This research tool will be the basis for future reports.

The largest proportion of the physicians involved have become friends of the program. Some are working hard to implement similar plans in other populations, notably among low-income groups and the poor. One result of such efforts is a multiphasic health check-up for 4600 migratory workers and persons in poverty areas in Stockton, California, implemented in the fall of 1970 under the auspices of California Regional Medical Program, Area III, Stanford University School of Medicine, and the San Joaquin

Medical Society. A small proportion of physicians are skeptical. A sizable proportion of the skeptics maintain an active and rational dialogue with the consultants and administrators of the program, and have contributed valuable criticisms. One reservation frequently expressed is whether the cost of discovery in terms of retrievable health compares favorably with the traditional periodic health examination by a physician. Without the evidence of abnormal findings provided by multiphasic testing, it is unlikely that members of the population group concerned would overcome their habitual resistance to consulting a physician except for extreme illness or acute crisis. The combination of mass education and group participation in multiphasic testing, with referral to a private physician for appraisal, appears to have been one logical and effective method of achieving the goal of bringing people under early care.

The testing program itself was made possible by the computer. No other method could have stored, processed and retrieved information in the quantities necessary to perform this operation. The computer's ability to handle data made possible the entry into medical care of thousands of persons who would otherwise have been unlikely to obtain care as they should: early in the course of disease, before crisis, by appointment with their personal physician, with assurance of follow-up and payment of services arranged with the utmost simplicity of bookkeeping for the physician.

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LETTERS *to the Editor*

Venereal Disease Education

To the Editor: The recent appearance of a spate of articles on gonorrhea, the completed report of the State VD Task Force, and the current drive for increased funds for vd control provoke me to voice my concerns about public health practices in regard to gonorrhea. Our educational efforts are based on insecure premises and half-truths and are failing to influence the behavior of the population at risk of cc. Our propaganda mixes statistics and facts and innuendoes, often combining syphilis and gonorrhea, though the only similarity between these diseases is their transmission by sexual intercourse. And our program for control is based on premises which are unproven in this or other similar infections.

First, in regard to venereal disease education, for years we have supported the thesis that vd can be taught as a unit on communicable disease and need not be combined with "sex" education. Such assertions are made in order to gain support of educators for vd instruction despite the emotional conflicts surrounding family-life or sex education. However, it seems patently ridiculous to hope to influence the sexual behavior of young people in a course on germs, statistics, and symptoms, while ignoring the life-style and value system that inevitably lead to exposure to the gonococcus. Furthermore our educational efforts too often involve scare tactics and half-truths. As in drug education the youthful audiences disbelieved when we painted dark pictures of dire consequences of smoking marijuana, so too do young people disbelieve when we elaborate on dread complications of gonococcal infection. They know they can smoke grass and not become a junkie; they also know they can have gonorrhea repeatedly with little morbidity or evidence of permanent damage. Finally, we are talking out of two sides of our mouths when we bewail sterility from gonorrhea, and extol sterility from pills and vasectomy.

For years we have been combining our data on syphilis and gonorrhea, lumping statistical totals and lists of complications to make them sound more impressive. Figures for unreported cases of vd are gleaned from quite unreliable mail survey data, but quoted extensively until they sound like irrefutable truth. Totals on syphilis cases include large numbers of people treated and probably reported ten or twenty years ago. We don't report a new case of tuberculosis because of a healed scar and a positive tuberculin, why report a new case of syphilis because of an old reactive serology? And figures on congenital syphilis are grossly swollen by late diagnosis of adults instead of measuring untreated infection in infants.

Current recommendations in gonorrhea control urge extensive mass screening programs in prenatal, family planning and gyn. clinics, in student health services and private physicians' offices to find asymptomatic carriers of gonococcus. We tried this sort of approach years ago screening for streptococcal carriers, and abandoned the practice. And although a fair percentage of the healthy population are carriers of meningococcus, no one is advocating mass screening for that organism. Still it must be admitted that strep and meningococcus, ubiquitous like the gonococcus, cause many more deaths than *Neisseria gonorrhoeae*. Complications from gonorrhea certainly do occur; and yet this disease, even with its wide dissemination (300,000 cases in California in 1970?), probably causes fewer days of illness and loss of work time than the common cold. I wonder if our enthusiasm for detecting asymptomatic harbingers of the gonococcus is more related to social disapproval of its means of transmission than to fear of its medical consequences—which when recognized respond dramatically to antibiotics.

There is no evidence to date that a massive infusion of funds and manpower to permit case interviewing and contact tracing on a state or nationwide scale will achieve real disease control.

The assumption that methods of syphilis epidemiology will succeed for gonorrhea, a totally different disease, is tenuous at best.

Diseases of public health importance have never been controlled by treatment alone. Prevention of gonorrhea by a vaccine is not possible at least at present. Unless we can convince the populations at risk that this is a health hazard of sufficient import to warrant such preventive techniques as we do possess, abstinence, the condom and possibly chemical prophylaxis, separation of host and disease agent seems highly unlikely. I do not mean to deny the seriousness of gonorrhea; data from pre-antibiotic days amply demonstrate its potential. I am concerned that we are pretending to wisdom we do not have and to medical solutions that are totally inadequate for essentially social behavioral problems. Let's get our facts straight, our education on human sexuality realistic, and our programs prevention oriented.

MARY RIGGS, M.D.

*Assistant Health Officer
Santa Clara County Health Department
San Jose*

An Earthquake Under Grass

To the Editor: I thought it might be of interest to physicians to relate an experience of treating a patient who was intoxicated with marijuana during the February earthquake. He is a 21-year-old senior at the local state college who was being seen for a success phobia. He had made a trip south to the border that night and returned home about 5:00 a.m. He woke up his (male) roommate and they had a joint for breakfast. Both were "high" when the earthquake occurred at 6:00 a.m. My patient reported that he was totally paralyzed. He could do nothing but sit in the chair. He realized what was happening but could not move. He became acutely anxious which led to further immobility. His friend got to the door but could not get it open. Normally he had no difficulty with this task but because of his intoxication he could not unlock it.

I would like to make several comments. The most obvious one is can anyone not understand why we are having difficulty in Viet Nam. The services have only recently begun to admit mari-

juaana use there when I have talked to ex-GI's coming back for "several years" who say that 90% of the troops have been regular users. How can we expect them to function in emergencies when they are paralyzed with this drug?

The marijuana users compare its effect with alcohol. Certainly a great amount of alcohol will cause such paralysis of action but it is usual in moderate alcohol intoxication for the person to "sober up" quickly when faced with an emergency. Soldiers for years have used alcohol to make them accomplish deeds of bravery.

We as physicians have led to some of this. LSD first came into use as a research drug to try to duplicate schizophrenic reactions. I believe our mistake was not recognizing early that we were not creating schizophrenic reactions or other exotic brain conditions that would "expand consciousness" but were causing acute and chronic brain syndromes. We had not seen delirium from the infectious diseases for a few years and had forgotten about it. Admittedly the delirium from marijuana is less severe on some occasions but can still cause hallucinations and usually causes other perceptual distortions especially time-space relationships. I feel organized medicine must take a strong stand to correctly diagnose these conditions and expedite careful research work to prove their functional brain disturbances and the hazards thereof.

JOHN C. SHIPPER
Sylmar

Progonasyl for VD Prophylaxis?

To the Editor: In an editorial, "Venereal Disease Epidemic" (August, 1971, Page 78), the author stated that an intravaginal proprietary preparation, progonasyl, could be used as a prophylactic agent. The regional office of the FDA advises that this preparation although "marketed for more than 40 years" is still an Investigational New Drug in terms of its venereal disease prophylactic properties.

Your readers might find it helpful if you qualified the status of other than fully approved drugs for the treatment indication described.

ERWIN H. BRAFF, M.D.
*Acting Chief
Division of Venereal Disease Control
San Francisco*

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Stephen M. Morris, President-Elect, American Hospital Association, Phoenix

Fred I. Gilbert, Jr., M.D., Medical Director, Straub Medical Research Institute of Hawaii, Honolulu

Donald A. B. Lindberg, M.D., University of Missouri School of Medicine, Columbia

Steven R. Yarnell, M.D., University of Washington School of Medicine, Seattle

Eleanor A. Brand, President, Board of Directors, Puget Sound Group Health Cooperative, Seattle

Howard Ulfelder, M.D., Massachusetts General Hospital, Boston

Felix Rutledge, M.D., M. D. Anderson Hospital, Houston

John L. Lewis, Jr., M.D., Memorial Hospital for Cancer and Allied Diseases, New York City

Georges P. Bergot, M.D., Medical Director, Orly Airport, Paris

Charles C. Gullett, M.D., Medical Director, Trans World Airlines, Kansas City, Mo.

Ludwig G. Lederer, M.D., Ph.D., Medical Director, American Airlines, New York City

George J. Kidera, M.D., Medical Director, United Air Lines, Chicago

Robert Fraser, M.D., McGill University Faculty of Medicine, Montreal

Arthur H. Keeney, M.D., Philadelphia

John S. Young, M.D., Phoenix

T. N. Evans, M.D., Acting Dean, Wayne State University School of Medicine, Detroit

PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H., Director, State Department of Public Health

Premarital Examinations For Syphilis

CALIFORNIA LAW REQUIRES applicants for marriage licenses to have premarital examinations for infectious syphilis not more than 30 days before obtaining a license. The California Administrative Code was amended recently to broaden the range of approved syphilis tests for premarital and prenatal examinations. Approved tests now include VDRL slide, Automated Reagin, Fluorescent Treponemal Antibody (absorption), Automated Fluorescent Treponemal Antibody, and the Rapid Plasma Reagin (eirele) Card tests. Any of these now constitutes a "standard test" as required by the California Civil Code and the California Health and Safety Code.

The increased incidence of infectious syphilis in California since 1969 makes finding infected premarital applicants more likely, particularly since prospective brides and grooms are largely young adults, in whom most syphilis is found. In 1970 the rate increased 37 percent and the upward trend continues into 1971.

Blood tests help find new infections, but a blood test alone does not satisfy the legal require-

ments. The physician is required to perform a physical examination on each applicant to determine the presence or absence of infectious syphilis. This includes taking an adequate history in which the physician questions the applicant concerning previous signs, symptoms or therapy for syphilis. The minimum physical examination should include visual inspection of the entire skin, including palmar and plantar surfaces, mucous membranes and the mucocutaneous junctions, particularly the oral, genital and rectal areas. Without a physical examination, communicable primary or secondary syphilis can be missed, particularly seronegative primary syphilis. Conversely, a reactive serology does not necessarily indicate infectious syphilis.

Syphilis of less than two years' duration is considered communicable to the marital partner and to offspring unless adequately treated. In female patients, untreated syphilis of even longer duration may be communicated to offspring. However, if the physician is assured that a syphilitic patient has had adequate treatment and is no longer infectious, it is permissible to sign the Marriage Health Certificate when it is returned from the laboratory.

Primary and Secondary Syphilis California 1960-1970

<i>Year</i>	<i>Cases</i>	<i>Rates/100,000</i>
1960	1,581	10.0
1961	1,605	9.8
1962	1,884	11.1
1963	2,142	12.2
1964	2,148	11.9
1965	1,995	10.8
1966	1,781	9.4
1967	1,706	8.9
1968	1,748	9.0
1969	1,795	9.0
1970	2,348	12.3

For those in whom syphilis is infectious, treatment with penicillin or other antibiotic for penicillin-sensitive patients should be completed before marriage. The possibility for infection and communicability should be explained to both partners. Upon request, local health departments will provide recommendations for treatment, and for serologic and spinal fluid follow-up.

Completion of treatment followed by one to two years of observation is a reasonable safeguard, although not providing absolute proof against transmission of syphilis. Patients and their marital partners should be urged to have follow-up examinations, including early prenatal care.

The marriage health certificate may not be withheld because of gonorrhea but physicians can use the opportunity offered by the physical examination to ensure that candidates are free from gonorrhea or other venereal or communicable diseases.

The State Department of Public Health distributes certificates and laboratory report forms upon application to all public health and clinical laboratories approved to perform tests required by the premarital law. Blank certificates are not issued directly to physicians.

For further information about these requirements, physicians may contact their local health departments.

X-RAY OPERATORS MUST HAVE CERTIFICATION

Physicians, chiropractors, and podiatrists who operate x-ray machines or supervise the operations of x-ray machines are required by law to obtain certification by January 1, 1972, according to Dr. H. C. Pulley, assistant director of the California State Department of Public Health and chairman of the Radiologic Technology Certification Committee. Certification of users is required in addition to registration of the machines, which has been required since 1962.

"The purpose of this law is to protect the people of California from excessive and improper ionizing radiation," Dr. Pulley said. "We have already certified x-ray technologists in the state and issued limited permits to persons qualified to perform limited x-ray procedures."

Applications for certification will be mailed in September by the Bureau of Radiological Health to all California licentiates using x-rays in their practice except dentists, who are regulated by a separate law.

The fee for initial certification is \$20. Annual renewal will be \$10.

Certificates will be issued to all applying licentiates who, before July 1, 1971, operated or supervised the operation of equipment properly registered with the State Department of Public Health.

Certification of licentiates (physicians, chiropractors, and podiatrists) is the third phase of implementation of Senate Bill 1056, passed by the state legislature in 1969, which provides for standards of experience, education, and training for all persons who use x-rays on human beings in California. The law is now contained in Sections 25660-25669.2, Chapter 7.4, "Radiologic Technology," of the California Health and Safety Code.

Information

Extracorporeal Circulation

Part I

ROBERT S. LITWAK, M.D.

*Material Supplied by the American
Heart Association*

THE SINGLE MOST IMPORTANT advance in the surgical management of heart disease has been the development of practical methods of performing direct vision operations within the heart using temporary extracorporeal circulation. Clinical success with such a method was first accomplished in 1953 by Dr. John H. Gibbon, Jr., who had spent the preceding 16 years developing physiologic concepts and equipment to achieve a goal which all but a few thought impossible. With proper utilization of existing equipment, a well executed operation and thoughtful post-operative care, an imposing list of cardiac abnormalities may be corrected in an unhurried fashion with considerable certainty that the patient will recover and be improved. Permissible periods of total cardiopulmonary bypass approximate 4 hours although the vast majority of intracardiac operations are completed in less than half that time.

Equipment and Methods

Temporary cardiopulmonary bypass is conducted with a variety of extracorporeal circuits, all of which possess (1) a means of pumping blood with minimal turbulence and (2) a device for gas exchange of venous blood withdrawn

from the patient so that oxygen and carbon dioxide tensions reflect those normally observed in pulmonary venous blood.

The most commonly used pump consists of one or two rotating rollers which compress a tube so that the contained blood is gently forced out. The output of these roller pumps is continuous and relatively non-pulsatile.

Three gas exchange mechanisms ("oxygenators") are in current use. Dispersion of oxygen bubbles in blood with subsequent defoaming (bubble oxygenators) and surface filming of blood on either a series of stationary vertical sheets or rotating discs in an oxygen-rich environment are the two most commonly employed systems because of simplicity and, in the first instance, the availability of cheap disposable units. The third type, a membrane "oxygenator," closely simulates conditions found in the natural lung by interposing thin gas-permeable membranes between the blood and an oxygen-rich atmosphere. This system minimizes protein denaturation which has been shown to be a consequence of the large blood-gas interface present when other "oxygenators" are used. Although early models were cumbersome and relatively inefficient, recent modifications have made these units increasingly practical for daily clinical use.

In practice, the heart-lung machine is usually primed with a mixture of heparinized blood and crystalloidal solution (hemodilution). Although conclusive data are lacking, clinical experience suggests that the diluted perfusate is advantageous because its lower viscosity improves tissue perfusion and diminishes blood trauma. The patient's blood is rendered incoagulable with heparin and cannulae are inserted into the venae cavae or right heart for diversion of venous blood into the extracorporeal apparatus. Return of oxygenated perfusate to the patient is accomplished with a cannula placed in the arterial circuit, frequently the ascending arch of aorta or a more peripheral vessel such as the iliac or femoral artery. At the onset of bypass, only a portion of the total venous return is diverted into the apparatus. This period of partial perfusion is used to check all portions of the circuit before definitive cardiac operation is commenced. Total cardiopulmonary bypass is achieved by tightening snares around the caval cannulae and the intracardiac operation is begun. Intracardiac blood of coronary and bronchial circulatory ori-

This article is to be published in two parts. Part II will appear in a subsequent issue.

Dr. Litwak is from the Division of Cardiothoracic Surgery, Department Surgery, Mount Sinai School of Medicine, New York City.

gin is gently aspirated into the apparatus, defoamed and returned to the patient. When the aortic valve is competent, the perfusion pressure provided by the apparatus maintains the valve in a closed position and assures satisfactory blood flow to vital organs. However, when the valve is distinctly incompetent or requires exposure for surgical correction, the ascending aortic arch is occluded, a proximal aortotomy made and coronary artery cannulation and perfusion carried out. Blood (and therefore body) temperature is controlled by passing the perfusate through a heat exchanger. Moderate hypothermia (30 to 32°C) is often used to reduce total body oxygen consumption, although recently there has been an increasing tendency to conduct perfusions at normothermic conditions.

Physiologic Requirements

The essential requirement of temporary extracorporeal circulation is that it satisfactorily replace the heart and lungs for a limited time. The need of the tissues for oxygen and the necessity for removal of carbon dioxide and other metabolites require that the perfusion rate and gas exchange be sufficient for such purposes. Although basal cardiac output in normal subjects approximates 3.1 L/min/M², it has been found that flow rates of 2.2-2.4 L/min/M² are satisfactory for perfusion periods up to 4 hours. With these flow rates, maintenance of mean systemic arterial pressures of 50 to 70 mm of mercury (in normotensive patients) is generally sufficient to assure satisfactory organ function during and after perfusion although reliable data concerning partition of blood flow to organs during whole body perfusion in man are not yet available.

An intraoperative fall in hematocrit, the consequence of perfusate dilution, is well tolerated

despite the reduced oxygen-carrying capacity of the blood, provided that flow rate, perfusion pressure and gas exchange are properly maintained. Systemic arterial oxygen and carbon dioxide tensions must be kept at essentially normal levels (100 and 40 mm of mercury, respectively). It is particularly important that hypocarbia be avoided because of its adverse influence on cerebral function.

Stability of the intracellular and extracellular environments requires consideration of need for therapy of the reduced buffering capacity of the blood which accompanies significant hemodilution. Incremental infusion of buffers, either sodium bicarbonate or tromethamine, are generally used during perfusion. The latter offers the advantage of a non sodium-containing ion which can traverse the cell membrane to provide both intracellular as well as extracellular buffering. Properly conducted whole body perfusion should not be associated with significant alterations in buffer base and hydrogen ion concentration.

Cardiopulmonary bypass is associated with alterations in vascular volume, water and electrolyte distribution which may contribute to morbidity and mortality of not properly appreciated. There is a measurable reduction of blood volume and the extracellular water is increased, although in the absence of pre-existing cardiac or renal failure this may largely be the result of intraoperative fluid administration during and after perfusion. Postoperative urinary excretion of sodium is low and potassium excretion high. Infusion of supplemental potassium (in the absence of Oliguria) will normally prevent postperfusion hypokalemia and its attendant danger of cardiac arrhythmias.

(Continued in Part II to be published in a subsequent issue)

In Memoriam

ADELSTEIN, LEO JOEL, Los Angeles. Died July 31, 1971 in Los Angeles of heart disease, aged 68. Graduate of Tufts College Medical School, Boston, 1925. Licensed in California in 1927. Doctor Adelstein was a member of the Los Angeles County Medical Association.



ALDEN, WARD CLAIR, Pasadena. Died July 22, 1971 in Vista, aged 84. Graduate of Chicago College of Medicine and Surgery, 1917. Licensed in California in 1931. Doctor Alden was a retired member of the San Bernardino County Medical Society and the California Medical Association, and an associate member of the American Medical Association.



BROPHY, JOHN R., Pasadena. Died July 29, 1971 in Arcadia of cardiac arrest, aged 68. Graduate of Jefferson Medical College of Philadelphia, 1927. Licensed in California in 1937. Doctor Brophy was a member of the Los Angeles County Medical Association.



CARLSON, CLIFFORD M., Santa Rosa. Died August 20, 1971 in Santa Rosa, aged 73. Graduate of The University of Oregon Medical School, Portland, 1926. Licensed in California in 1926. Doctor Carlson was a member of the Sonoma County Medical Society.



CARMAN, HENRY F., JR., San Francisco. Died August 11, 1971, aged 63. Graduate of Northwestern University Medical School, Chicago, 1934. Licensed in California in 1939. Doctor Carman was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.



ECKERLE, WILLIAM JOSEPH, Torrance. Died July 11, 1971 in Torrance of cerebral vascular accident, aged 82. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1922. Licensed in California in 1922. Doctor Eckerle was a member of the Los Angeles County Medical Association.



ECKERT, JOHN ROSS, Visalia. Died July 31, 1971 near Visalia, aged 57. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1942. Licensed in California in 1942. M.D. degree from California College of Medicine, 1962. Doctor Eckert was a member of Tulare County Medical Society.



JOHNSON, JAMES KNOX, Culver City. Died August 6, 1971 in Santa Paula of heart disease, aged 79. Graduate of Chicago College of Medicine and Surgery, 1916. Licensed in California in 1934. Doctor Johnson was a member of the Los Angeles County Medical Association.

LIU, DAVID C. (CHING T.), Walnut Creek. Died August 4, 1971 in Walnut Creek of metastatic carcinoma, aged 60. Graduate of China Union Medical College, Peiping, 1938. Licensed in California in 1954. Doctor Liu was a member of the Alameda-Contra Costa Medical Association.



LOEWENSTEIN, WILHELMINA, San Francisco. Died August 1, 1971, aged 87. Graduate of Medizinische Fakultät der Universität, Vienna, 1914. Licensed in California in 1939. Doctor Loewenstein was a member of the San Francisco Medical Society.



MICHAEL, PAUL P. E., Monterey. Died August 3, 1971 in Carmel, aged 70. Graduate of McGill University Faculty of Medicine, Montreal, 1928. Licensed in California in 1928. Doctor Michael was a member of the Monterey County Medical Society.



MILLER, FREDERICK C., San Bernardino. Died August 7, 1971 in San Bernardino, aged 85. Graduate of University of Illinois College of Medicine, Chicago, 1912. Licensed in California in 1943. Doctor Miller was a retired member of the San Bernardino County Medical Society and the California Medical Association, and an associate member of the American Medical Association.



POHLMAN, MAX EDWARD, Los Angeles. Died July 31, 1971 in Orange County of injuries received in an automobile accident, aged 59. Graduate of St. Louis University School of Medicine, 1934. Licensed in California in 1936. Doctor Pohlman was a member of the Los Angeles County Medical Association.



ROBBINS, ARTHUR C., JR., Redlands. Died August 8, 1971 in Redlands, aged 47. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1954. Licensed in California in 1955. Doctor Robbins was a member of the San Bernardino County Medical Society.



VAIL, JAMES B., Santa Cruz. Died July 31, 1971 of cancer, aged 75. Graduate of The University of Minnesota Medical School, Minneapolis, 1921. Licensed in California in 1943. Doctor Vail was a retired member of the Santa Cruz County Medical Society and the California Medical Association, and an associate member of the American Medical Association.



WYNE, PAUL SAMUEL, San Francisco. Died August 13, 1971 in San Francisco of heart disease, aged 69. Graduate of Hahnemann Medical College and Hospital of Philadelphia, 1926. Licensed in California in 1927. Doctor Wyne was a member of the San Francisco Medical Society.

BOOK REVIEWS

CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

CARDIOVASCULAR DYNAMICS—Third Edition—Robert F. Rushmer, M.D., Director, Center for Bioengineering; Professor and Head, Division of Bioengineering, School of Medicine; Professor of Bioengineering, College of Engineering, University of Washington, W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1970. 559 pages, \$20.00.

This third edition is an extensive revision of Dr. Rushmer's original text, "Cardiac Diagnosis: A Physiologic Approach." It represents an attempt to relate, in a single volume, basic cardiovascular physiology to clinical diagnosis. There is a new section on arterial hypotension and shock, and newly rewritten chapters by guest authors on the coronary system, the electrical activity of the heart, and on valvular heart disease. The volume, however, while generally good, is not of uniform high quality; the most serious objection being lack of depth. In Chapter I, for example, "Properties of the Vascular System," blood volume is barely touched upon. In Chapter II, there is a new and welcome seven-page section, "Development of the Normal Heart"; this would be of greater help had the author included an illustration of the developmental aortic arches. The section "Causes of High Blood Pressure" was disappointing in its superficiality, particularly with regard to the exciting hormonal discoveries of the past decade. All adrenal and renal mechanisms are allocated a scant three pages; angiotension is given one paragraph in a different section; the prostaglandins are not mentioned. The most recent bibliographic paper, of which Dr. Rushmer was a co-author, dates from 1967. There is a nicely rewritten section on cardiovascular responses during exertion in man, partly correcting a deficiency in the earlier edition, which primarily described animal studies.

The strongest parts of the book, as in the previous edition, deal with hemodynamic mechanisms and the physics necessary for proper measurement and understanding. There are lucid descriptions and illustrations, helpful to the clinician. In summary, even with its deficiencies this book will serve as a useful reference to students and clinicians, particularly to those now beginning their training in clinical cardiology.

LUCY S. GOODENDAY, M.D.

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AMERICAN MEDICINE IN CRISIS—Edward P. Luongo, M.D. Philosophical Library, Inc., 15 East 40th Street, New York City (10016), 1971. \$9.95.

About every year or so for about the last dozen years, another book appears having to do with the health scene in the United States and, in general, the tone has been to down-grade the physicians who help deliver the care.

Most of these books have been received with horrendous boredom and are gathering dust on library shelves.

These are reminiscent of the remark Henry Kaiser made when he told the press that he didn't really enjoy losing several hundred million dollars in his ill-fated venture in producing automobiles, but he was disappointed that when you threw a pebble that size into a pool, it didn't make a bigger splash.

The recent "American Medicine in Crisis" by Dr. Ed-

ward P. Luongo, formerly Professor of Preventive Medicine at UCLA and now serving in a comparable capacity at Georgetown University, should make more of a splash.

In a humorous, articulate and tongue in cheek manner, he comments on the medical scene and, particularly, comments on the fact that all health problems are not solved by physicians but are corollary to the problems of ignorance and superstition and fear.

It isn't the physician's fault that some of the worst medical care in the world is within a block or two of the great medical centers. The crisis seems to be somewhat a matter of definition and as when the late John Foster Dulles arrived at the airport and was asked where he wanted to go he replied, "Take me anywhere, there is a crisis everywhere."

One gets the impression that Dr. Luongo views the planners with some amusement. Having been involved in many meetings with planners myself along with others, I often wonder who is home minding the store. Presumably, even poor planning is analogous to dyspareunia which is said to be better than no pareunia at all.

He comments with much charm that medicine is still an art and it is about time to talk back to the computers, who would make medicine a skilled trade rather than a way of life.

Of particular interest is the fact that he deplores the situation today wherein the doctor becomes an advocate and if he isn't willing to more or less stretch the truth for his patient, he loses the good will of the patient and this is, naturally, true when litigation is involved. The advocate system has always seemed stupid to doctors since they are accustomed to fighting the common enemy of disease and have a suspicious feeling that the ends of justice are not determined in the advocate system by the facts but by the skill of the advocate.

Dr. Luongo's plea for more training in the humanities for doctors and emphasis on the wide and intelligent use of leisure is a delight. He does not advocate the return to practicing medicine by instinct but speaks well for the combination of humanitarianism and technical skill, which the ideal physician should have.

WILLIAM F. QUINN, M.D.

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A SYNOPSIS OF PHARMACOLOGY—Second Edition—V. C. Sutherland, Ph.D., Professor of Pharmacology, University of California, San Francisco, W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1970. 720 pages, \$10.75.

In its second edition, this synopsis has grown from 267 to 720 pages, reflecting the amount of new information made available in the last eleven years. The organization of chapters leaves much to be desired. For example, while the discussion of analgesics and anesthetics (including local anesthetics) under the heading of agents affecting the central nervous system may be acceptable, discussion of such drugs as colchicine, indomethacin, probenecid, allopurinol, and gold salts (and their actions in gout and rheumatoid arthritis) is clearly out of place in this chapter.

Anticoagulants, hemostatic agents, fibrinolytic agents, etc., are included on a chapter on hematics. Antimicrobial agents are discussed in four chapters, but are grouped in a rather peculiar way. The parenteral (and topical) use of aminoglycosides—among our most valued parenteral compounds—is discussed in a section entitled “Topically Effective Antibiotics.”

The format is that of an outline. Specificity and accuracy are crucial with this type of presentation so as to avoid misinterpretations. This is particularly true since this book is aimed primarily at students. Unfortunately, the book does not live up to these requirements. Some of the information, in the format provided, can be misleading. Thus, in Chapter 13 one can easily be misled to believe that organisms such as Group A β -hemolytic streptococcus, pneumococci and meningococci develop resistance to penicillin G, or that the use of 15 to 20 mg/kg/day of *parenteral* neomycin is an accepted form of antimicrobial therapy. The chapter on “Autonomic Nervous System Agents” seems to accomplish its purpose. It is clear and concise with simple figures.

This textbook, we feel, can be of some help to the clinician who desires to review the subject of pharmacology. It is not suitable for students who will generally be unable to evaluate the information presented in a critical fashion.

JACOBO SABBAJ, M.D.

TUMOURS OF THE TESTICLE—John P. Blandy, D.M., M.Ch., F.R.C.S., Professor of Urology at the London Hospital Medical College, Consultant Urological Surgeon to the London Hospital and St. Peter's, St. Paul's, and St. Philip's Hospitals, London; H. F. Hope-Stone, M.B., B.S., D.M.R.T., F.F.R., Consultant Radiotherapist, the London Hospital; and Anthony D. Dayan, B.Sc., M.D., M.R.C.P., M.R.C.Path., Consultant Pathologist, the Hospital for Sick Children, Great Ormond Street, and the National Hospital, Queen Square, London. Grune & Stratton, Inc., 757 Third Avenue, New York, N.Y. (10017), 1970. 199 pages, \$7.00.

This monograph from England represents a joint venture by an urologist, a pathologist and a radiotherapist. Each has covered his aspect of the problem in very satisfactory form. An additional chapter on chemotherapy is most likely done by Blandy, the urologist, and is quite adequate for this rapidly changing field. There are many tables of statistics. Some of these serve to emphasize the wide range of reported experience, particularly with reference to prognosis. Granted that the age factor is more significant with military source material, one is deeply impressed with the urgent need of more uniform tissue definition. Until this is achieved it will be very difficult to draw comparative conclusions between different series. However, the tables of statistics do offer a ready source of reference to the material that is now available.

The bibliography is extensive and the index quite adequate. The illustrations are not of the highest quality, perhaps the fault lies with the printing. But the modern surgeon no longer depends upon drawings as the primary source of his surgical technic.

The primary clinical source material referred to in this monograph comes from the records of the past eighty years at the London Hospital. In addition the authors make extensive reference to the material and the experience collected by the English Testicular Tumor Panel and Registry. (Throughout the text this is referred to by the initials TTPR and in similar fashion the initials for tumor types according to the English system are used freely. It behooves the American reader to become familiar with the English terminology and the relevant initials used.) All this is reasonable. However, in again presenting the English and the American testicular tumor classification systems side by side, one is impressed by the unnecessary, if not ridiculous, differences of terminology used in our two

English speaking nations. Surely it is high time for our respective pathologist bodies to review these tissue specimens together, make such concessions as are needed and come up with one mutually acceptable classification schema. This criticism is not aimed at the authors, however, for they confess to their own confusion. This monograph is a good one and should have wide usefulness.

THOMAS F. CONROY, M.D.

THE FOUNDERS OF NEUROLOGY—Second Edition—One Hundred and Forty-Six Biographical Sketches by Eighty-Eight Authors—Compiled and Edited by Webb Haymaker, Senior Scientist, National Aeronautics and Space Administration, Ames Research Center, Moffett Field, California; and Francis Schiller, Associate Clinical Professor of Neurology, Lecturer in History of Health Sciences, University of California Medical Center, San Francisco. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill. (62703), 1970. 616 pages, \$18.00.

More than most medical fields, neurology is strewn with names of the great ones of the past. For some, these figures are merely eponyms to stumble over; for others, they are signposts on the highroad of scientific progress; for a few, they are monoliths to be worshipped. This biographical collection offers something for every kind of neurologist. It is a lighthearted and informal glimpse into the careers of one hundred and forty-eight “founders” of neurology. (Some of the subjects are familiar greats, but many neurologists will not recognize dozens of names.) Although each sketch is only two or three pages long, the authors have managed to provide a pleasing balance of piquant personal detail, scientific history, and catalogued accomplishments. The biographical approach allows the scientist's best-known work to be seen in the context of his other efforts and of contemporary influences. Many sketches are first-hand accounts by friends of the subjects, and the quality of writing is unusually high thanks to the polishing and individual contributions of the two editors. A brief reference list after each article cites original publications and biographical sources, enabling the interested reader to delve further.

ROBERT B. LAYZER, M.D.

THE CLINICAL RECOGNITION OF CONGENITAL HEART DISEASE—Joseph K. Perloff, M.D., Professor of Medicine, Chief Consultant in Pediatric Cardiology, and Lecturer in Physiology and Biophysics, Georgetown University School of Medicine, Washington, D.C.; Consultant, Veterans Administration Hospital, Washington, D.C.; National Heart and Lung Institute, Bethesda, and Hospital for Sick Children, Washington, D.C. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105). (No price given)

The Clinical Recognition of Congenital Heart Disease is a relatively short textbook of congenital heart disease by comparison with others in the field. The stated intent was to provide information regarding congenital heart disease which did not confine itself to children or adults but included all age groups. Unfortunately, the book does not fulfill this promise since it contains relatively little information regarding the natural history of each lesion in the adult. This is truly unfortunate since a book which would characterize the latter natural history of congenital cardiac lesions would be extremely useful. This information is widely scattered today. Additionally, it is disappointing that the author does not utilize the newer and now well accepted terminology introduced in 1964 by Richard Van Praagh¹ for cardiac malpositions and transpositions. There is little discussion regarding the surgical approach, philosophy, or results in congenital cardiac disease. On the positive side, I found many of the schematic illustrations of the forms of heart dis-

¹*Anatomic Types of Congenital Dextrocardia*, Richard Van Praagh, M.D., et al. *The American Journal of Cardiology*, April, 1964

ease exceptionally well done. These diagrams might be very useful for student and house officer teaching. Additionally, Dr. Perloff presents far more than the usual number of X-rays, most of them very well produced and fairly classical for the conditions described. Finally, he discusses the arterial and jugular venous pulse as well as the phonocardiogram and auscultatory findings in each condition. Omitted is a detailed discussion of the physiology of the condition.

In summary, it would have to be concluded that if one were to have only a single textbook of congenital cardiac disease, this one would probably not be a wise choice. Even the brief attention given to the problems faced by the adult with congenital heart disease is not too different from that described in more comprehensive textbooks of congenital cardiac problems. I believe that the individual who might be most interested in this book would be one who teaches cardiology to students since the illustrations are of considerable teaching value.

STANLEY J. GOLDBERG, M.D.

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BLEEDING PROBLEMS IN CLINICAL MEDICINE—Armand J. Quick, M.D., Marquette School of Medicine, Milwaukee. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1970. 225 pages. \$9.50.

By emphasizing the evolutionary development of hemostasis Dr. Quick brings a rational approach to understanding the bleeding problems seen in clinical medicine. He emphasizes the fundamental importance of vascular hemostasis and the secondary and tertiary importance of cellular (platelet) and coagulation mechanisms. He outlines the tests that he feels are most meaningful clinically. The known bleeding disorders are classified as vascular, cellular (platelet), or coagulation defects and are discussed in this framework by means of exemplary case presentations. These case presentations and his discussion reflect his vast personal experience and constitute the unique strength of this book.

The orientation is clinical and pre-supposes a fundamental knowledge of clotting mechanisms, platelet function, and laboratory techniques. The chapter on diagnostic tests is short and might well have been divided into preliminary paragraphs preceding the chapters on vasopathy, thrombopathy, and coagulopathy. Considering the wide use of the partial thromboplastin time, bleeding time and thrombin time, a discussion of these tests would seem desirable. The chapter on salicylates, though interesting, was not relevant to his main theme, and the pertinent points could have been emphasized under his discussion of the aspirin tolerance test. This small amount of reorganization of the material could have materially strengthened the total message.

The book is of great value to the medical student for its emphasis on the evolutionary approach to hemostasis. It is of equal value to the advanced student of clinical hematology for its concise discussions of illustrative cases drawn from Dr. Quick's personal collection.

LEONARD SCHUTZ, M.D.

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OVERCOMING THE FEAR OF DEATH—David Cole Gordon. The Macmillan Company, 866 Third Avenue, New York, N.Y. (10022), 1970. 115 pages, \$3.95.

Recently there has been the appearance of a number of books and articles dealing with various aspects of death—its definition, its effect on the terminal patient and his family, etc. *Overcoming the Fear of Death* deals with the subject of death from a philosophical and metaphysical point of view. It would appeal to someone interested in

the two main themes: (1) The frenzied existence we lead in life secondary to the fear surrounding the finitude of death and, in contrast, (2) the metaphysical appeal of the transcendent unity considered inherent in death. The author, David Cole Gordon, has a background in law and psychology. This short book (less than an evening's reading) would appeal most to a physician who has few spare moments but who is interested in a general philosophical approach that is only indirectly connected to the clinical problems of death. After reading the book, I found it readable but somewhat overstated.

I would agree with Mr. Gordon's initial thrust: Much of a man's life is led as if immortality or a synthetic representation of it were possible. (Monumental works are considered in this second category.) If the fear of the loss of immortality—death—were overcome, it follows that life would be richer. I fear, like much that resembles psychological panacea, it is interesting on a global scale but falls short as a means of dealing with many of the examples given by Gordon, such as putting forth the thesis that men who professionally chance death are some of the healthiest men alive. The example *summa cum laude* is "... Don Alfonso Cabeza de Vaca y Leighton, 17th Marquis de Portago, who died in 1957 while racing his Grand Prix car in the Mille Miglia in an accident that killed 11 persons and cut him in two at the age of 28." His other feats of athletic and sexual daring-do are spelled out. Gordon summarily dispenses with "... the 'profound' psychoanalytic insight that he was in love with death." I would suggest that Mr. Gordon is as guilty of doctrinaire conjecturing when he zealously applies the seeking of the unification experience as *the* motivation. Though frustrating, is it not true that as complex as man's symbolic processes are, the Marquis may have led his colorful life for any of a myriad of reasons that could only be approximately ascertained after much self study? Enough of Gordon's application of the basic motivation of unification seeking is Procrustean as to become tiresome.

The second thesis—the metaphysical appeal of death—appears with ever growing strength in the last third of this short book. Mr. Gordon feels that the basic motivation of humans is a quest for the unification experience, the essence of which is described as "... the spontaneous halting, not only of specific thought but of the very process of thought and intellection, as well as loss of self." Death is considered the epitome of this state. There is some difficulty with his stance which I will depict in the following paragraphs.

Mr. Gordon builds his unification experience primarily around the orgasmic experience and secondarily around the experience of anger and dangerous sports. The link between all three states is the build-up of tension with a succeeding release that is characterized by metaphysical unity and no thought. As described, the unification experience contains much of what man fears about death and attempts to avoid in life: Loss of time, self, thought.

The main difficulty with *Overcoming the Fear of Death* is the "proof" of the desirability of death. Gordon puts forth the view that we really should greet death as the ultimate unification experience, an experience characterized by the shedding of our egoistical uniqueness, so carefully built and tenaciously held, and by the lack of thought, intellection, as are the climactic moment of orgasm and its analogues. I quote from the last page:

"We do know what death is. Does not everything we know about the condition of death accord and confirm with what we know about the experience of unification? And is not this experience the one man most avidly seeks during his lifetime? Should he not welcome it when it comes? Is it not something which he

is quite familiar with, having tasted it many times during his lifetime? Why should he fear what is apparently a permanent condition and state of unification? The point of this book is that what we think we dread above all else is really what we most desire."

We do not know what death is—certainly not in the sense of sentient beings who can experience it, for certainly a fundamental and keystone difference between the examples of unification described and death is that the examples cited, particularly orgasm, are experiences, albeit ineffable; whereas, there is nothing to lead one to conclude that death is an eternal sentient experience. The rest of the points falter around this important distinction.

Much of philosophy struggles with the purpose of life and the purpose of death. The existential approach sees death as evitable and life without answers. With this as a point of departure, I can readily understand the necessity for a comforting explanation of life and particularly its termination. This is the place of Gordon's short book—interesting but incomplete and most fit for brisk reading about Western man's hope that there is substance to the Eastern metaphysical wish for transcending unity and death.

ARTHUR M. HOFFMAN, M.D.

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UROLOGICAL SURGERY—Fourth Edition—Austin Ingram Dodson, Jr., M.D., Associate Professor of Urology, Medical College of Virginia; Urologist to St. Elizabeth's Hospital; Urologist to St. Luke's Hospital and McGuire Clinic; Urologist to Crippled Children's Hospital, Richmond, Va. The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1970. 617 pages, with 694 illustrations, \$32.50.

This textbook purports to inform urologists of the advances in their field of surgery. In fact it is a large, warmed-over dish of obsolete material to which has been added the spice of some new chapters written by respected and able authors.

The organization of the material into forty-seven chapters is disconcerting. Entire chapters are set aside for such minor topics as "nephroptosis" and "aneurysm of the renal artery," and fully seven chapters to surgery of "the ureter," but only one chapter, next to last, is presented on prostatic surgery. Ominously, the last chapter is devoted to postoperative male incontinence.

Even more disturbing is the presentation as current and acceptable of various procedures which are, at best, historical curiosities and may well be judged by many to be dangerous. Thus in describing nephrectomy, mass ligation of the pedicle is advocated and further "occasionally . . . the clamps may be left on the pedicle and the wound is closed around them" (p. 206). For undescended testis the Bevan operation is recommended, the skeletonizing of the vessels of the cord in the inguinal canal; and that procedure, which unnecessarily risks infarction of the testis, is to be done "after puberty"—which probably eliminates the possibility of spermatogenesis from that testis. The non-surgical measures advocated in most of the chapters are woefully out of date—e.g. there is no mention of penicillamine or allopurinol in stone management, no mention of adrenergic blockade in preparing pheochromocytoma patients for surgery, no mention of antifibrinolytic therapy in prostatic bleeding.

Bright spots are the new chapters on "Use of bowel in urological surgery" and "Urethroplasty for stricture" by J. J. Murphy and "Surgery of bladder carcinoma" by Prout. These are outstanding, although they deserve better illustrations, and are recommended to old and new urologists. But even the strongest spice cannot make this textbook palatable.

R. F. GITTES, M.D.

CURRENT DERMATOLOGIC MANAGEMENT—Edited by Stuart Maddin, M.D., Clinical Instructor, Division of Dermatology, Department of Medicine, Faculty of Medicine, University of British Columbia; Active Staff, Vancouver General Hospital, Vancouver, British Columbia; Drug Consultant, Terence H. Brown, B.S.P., M.S., Ph.D., Associate Professor, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia. C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. (63102), 1970. 330 pages, \$38.75.

This is a book which follows the trend of having one editor and many contributors (176). Some contributing authors are nondermatologists.

The stated aim is to supply practical assistance in the management of skin diseases for dermatologists, pediatricians, general practitioners, internists or any branch of medicine. The subjects are covered by short discussions, mostly involving therapy along with a few current, pertinent references. This aim is accomplished in a readable manner interspersed with notes by the editor.

The text is divided into three parts. The first, *Dermatologic Procedures*, is a short section covering the use of essentially the physical modalities. The editor's cautioning note regarding the danger of using electrosurgery in persons wearing a pacemaker is timely.

Although this book is intended also for the nonspecialist in dermatology, the discussion of "Topical therapy with cytotoxic agents, 5-fluorouracil" can only be evaluated by an expert. This is apparently recognized by the editor using covering notations.

The section on cryotherapy should include a note on a set of variable sized brass applicators which is being marketed. These are used to deliver the effect of liquid nitrogen in a more exacting manner than the usual cotton on a wooden stick.

The second and the main body of this book covers *Therapeutic Management*. The various diseases are covered alphabetically. The texts are short and concise, and each is followed by a few recent key references. If one remembers that every man considers himself an expert in therapy, there are bound to be omissions. This book is meant to be more current in its approach to therapy rather than exhaustive.

The active dermatologic practitioner will recognize that some of the authors are more hospital-oriented in their approach to therapy. This is especially true in the section on bacterial infections. It is difficult for those who have treated penicillin reactions over the years, to recommend this drug except in some limited instances.

Considering what has been written about DDT, it is surprising that this drug would be recommended for pediculosis in the section on anogenital pruritis.

Any future edition should include a section on neurodermatitis. This is not adequately covered in the present edition under atopic dermatitis or among the limited conditions covered in the text under psychocutaneous disorders. A section on burns should be included because the dermatologist is often called upon to treat these, especially in the acute phase. Alopecia mucinosa should be considered along with mycosis fungoides. The difficulty of diagnosing some forms of oral carcinoma in spite of repeated biopsies deserves mention. The deletion of Glanders and Tungiasis would seem to be in order.

The third part, *Drug Index*, is an excellent idea and should be expanded. This portion is a must for anyone who graduated from medical school more than ten years ago. The drug index is edited by a member of the pharmacology department, University of British Columbia. The grouping and interrelationship of the newer drugs is shown through formulas, using chemical and proprietary designations.

WALTER R. NICKEL, M.D.

Indications for Coronary Arteriography

Risks vs. Benefits

ARTHUR SELZER, M.D., WILLIAM L. ANDERSON, M.D., AND
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■ *Coronary arteriography has become a diagnostic procedure which is no longer limited to major medical centers but is being performed in many community hospitals. The procedure carries an appreciable risk, which is only justifiable by specific benefits to the patient. The benefits are related to the potential availability of newer surgical procedures of bypassing obstructive coronary arterial lesions. A specific set of criteria for the performance of coronary arteriography has been developed from a critical analysis of the ratio of risk to benefit. A survey of the risk of coronary arteriography indicates that mortality increases at least twentyfold and morbidity sixfold when this procedure is performed in laboratories with a low caseload as compared with high caseload institutions. Thus there appears to be no justification for performing coronary arteriography in the absence of proper team facilities.*

AMONG RECENT ADVANCES in diagnosis of cardiac disease, coronary arteriography is playing an ever increasing role. Enthusiastic reception of this method of study of coronary artery disease may have swept the pendulum far beyond the center, perhaps even beyond a reasonable position. There are voices expressing the view that coronary ar-

teriography should have as wide an application as the use of the electrocardiogram or the plain chest roentgenogram in the routine diagnostic evaluation of the cardiac patient. Such recommendations overlook the obvious fact that the latter two procedures apply non-invasive techniques, while coronary arteriography is an invasive method of study with a morbidity and mortality among the highest of diagnostic procedures, and that its cost runs on the average 25 to 50 times higher than the simpler examinations. Any diagnostic procedure that carries a risk must have

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this risk balanced by measurable benefits. It is the purpose of this article to review the relationship between the risks and benefits of coronary arteriography and to derive hence a reasonable and prudent set of indications for its performance.

Technical Considerations

At present the selective technique of coronary arteriography, which requires direct injection of the contrast medium into each coronary artery, is the one almost exclusively used. Developed by Sones, this technique involves introducing specially designed cardiac catheters into the arterial system in retrograde manner and manipulating them under fluoroscopic control into each of the coronary ostia. There, a small amount (2 to 8 ml) of a contrast substance is injected for each of the multiple rotational views of the coronary tree. According to the original Sones technique, the catheters are introduced through a cut-down of a brachial artery. The modification of Judkins uses percutaneous introduction into the femoral artery by the Seldinger guidewire technique. Either cineangiography or cut-film angiography is used to visualize the flow of the contrast material through the coronary system. The choice between cineangiography and large film angiography involves deciding whether one would rather have the opportunity to observe dynamics of fluid motion in relationship to cardiac contraction, or better resolution of minute details. Most centers use either of the two methods; in a few both methods are used in the same patients during the same study. These two methods are complementary, rather than competitive.

With either method, satisfactory examinations depend on adequate facilities. Appropriate standards for radiographic equipment, processing facilities and personnel have been well defined, as well as the substantial expense of equipping and operating such a diagnostic laboratory and the economic consequence of underutilization.¹

Coronary arteriography may be performed as a separate procedure, or may be combined with other invasive diagnostic tests. The commonest additional procedure used in conjunction with it is left ventriculography, which involves injection of the contrast material into the cavity of the left ventricle for the purpose of the study of left ventricular wall motion and ventricular volumes as well as the competence of the mitral valve. Occasionally coronary arteriography is also performed

TABLE 1.—Results of an informal survey of coronary arteriography in the San Francisco Bay Area.

	Number of cases	Deaths	Death rate (percent)
Hospital A	700	7	1.0
Hospital B	650	3	0.5
Hospital C	500	3	0.7
Hospital D	200	4	2.0
Hospital E	25	2	8.0
Hospital F	50	1	2.0
Total	2,025	20	1.0

TABLE 2.—Results of an informal survey of coronary arteriography in a western city, including its medical school. Total number of procedures—800.

	Death rate (percent)
Hospital A	2.0
Hospital B	2.0
Hospital C	3.0
Hospital D	3.7

in conjunction with right heart catheterization, where a more complete study of cardiac dynamics at rest and during exercise may be included, if it is indicated.

Risks

The risks of coronary arteriography should be discussed under three headings: (1) The risk of dying directly as a result of the procedure; (2) The risk of serious complications with or without permanent sequelae; (3) The risk of lesser complications, causing discomfort and prolonging hospital stay and expense.

Accurate figures concerning deaths and complications from coronary arteriography are difficult to obtain for obvious reasons. The best figures are those obtained by a cooperative study under the auspices of the American Heart Association.² Out of 3,300 coronary arteriographic studies there were three deaths, a mortality rate of 0.1 percent. However, 80 percent of these procedures were performed at a single institution, so that they represent primarily a risk of a large-volume institution.

Supplementary data were obtained by one of us (HWM) in an informal inquiry into fatalities resulting from coronary arteriography in the San Francisco Bay Area and in a western university city. These figures are presented in Tables 1 and 2. It is evident from these figures as well as from the American Heart Association cooperative study that the risk of coronary arteriography declines

sharply with the increase of a caseload in a given laboratory. One gets the impression that there are turning points in the risk curve. The first turning point may be at about 200 arteriographies. The risk may then further decline after 500 to 1000 procedures have been performed by an arteriography team.

A further support of a presumption of high risk at low-caseload institutions can be found in the figures of the Heart Association cooperative study² dealing with non-fatal complications of coronary arteriography. In it the overall rate of complications was 1.9 percent; however, complication rate at the high caseload institution that supplied data on 2,700 cases was 1.0 percent; the combined rate of all other institutions supplying the remaining 600 cases was 6.1 percent. No statistical analysis of these figures is necessary to see their significance.

Improvement in the composition of the contrast substances have made them virtually non-toxic, except for rarely occurring true allergic reactions. The risk of coronary arteriography is thus related mainly to the manipulation of the catheter. It involves the following factors: (1) formation of a thrombus at the site of the introduction of the catheter or upon the catheter tip; (2) tear of the intima, producing dissection of the coronary artery; (3) damage to an atheromatous plaque; (4) unusual accidents, such as breakage of a guidewire or of a catheter; (5) hypotensive episodes related to the procedure, occurring in susceptible persons.

Fatal complications include: (1) the production of a fatal myocardial infarction; (2) "pump failure" probably due to early stages of myocardial infarction induced by the procedure; (3) intractable arrhythmias, also probably related to irreversible ischemia; (4) fatal non-coronary embolic complications (stroke).

Non-fatal, major complications include the production of myocardial infarction, cerebral vascular accident and vascular occlusion of extremities leading to gangrene. The commonest of "minor" complications is thrombus formation at the site of the introduction of the catheter, requiring thrombectomy.

The likelihood of complications increases with the severity of the patients' atherosclerotic disease—coronary and general—and with the advanced stage of myocardial involvement. However, some of the fatal complications have occurred in pa-

tients without significant cardiac disease who were being investigated for pain suspected of being coronary in origin. On the other side of the coin, coronary arteriography has been performed repeatedly without complications in our laboratories, without incident in a large number of seriously ill—often moribund—patients such as those with pre-infarction angina, in the early stages of acute myocardial infarction, even in cardiogenic shock. In such patients the imminence of life-saving surgical intervention contingent upon obtaining crucial diagnostic information made the higher risk of the procedures entirely justifiable.

Thus, it is clear that a patient undergoing coronary arteriography is undertaking an appreciable risk of death and serious illness. It is probably unnecessary to state that each patient needs to be made aware of this risk. In the present day of medical hucksterism—when diagnostic and surgical procedures are being sold to the medical profession and the lay public alike—"ideal" risk figures attained at a Midwestern clinic with "mass production" are often quoted. Since the great mass of coronary arteriograms throughout the country is being performed in low-caseload laboratories in community hospitals, such risk figures are irrelevant, and—to put it mildly—misleading.

Interpretation

Several factors can influence the interpretation of the coronary arteriogram. Among them, technical factors play an important role. An "ideal" film for interpretation depends first of all upon the basic equipment available for filming. The quality of the x-ray tube, of the intensifier, the film changer, and the camera is important. Equally important are items of technique in the performance of the test—the number of injections of the contrast medium into each coronary artery in order to visualize it in various rotational views, the proper centering of the radiographic beam, the size of the field, optimal processing, and others. Even in the most active laboratories with the best available equipment the quality of the film is not always the same: Maladjustment or malfunction of the radiographic apparatus, or malfunction of the processor may render the film with too much or too little density or contrast. Ciné films are ordinarily viewed after the procedure is terminated. A repeat film could only

be obtained by subjecting the patient to an entirely new procedure, which would not be justified in the case of a suboptimal, but still readable film. The second important factor in the interpretation of coronary arteriograms is the skill and experience of the reader. The process of film reading is a subjective interpretation of qualitative changes in the coronary artery, which—unlike some quantitative laboratory determinations—cannot be measured or expressed in exact numbers.

Abnormalities of the coronary arteries fall into three categories: (1) complete occlusion of branches, (2) partial occlusion by discrete plaques, (3) diffuse areas of narrowing or irregularity of coronary branches. Abnormalities of each type may be difficult to demonstrate and evaluate; such difficulties can only be resolved by a reader with wide experience with normal morphologic features and their variations, as well as with full awareness of all pitfalls and technical artifacts.

Among the most controversial aspects of the interpretation of coronary arteriograms are cases with suggestive or incontrovertible clinical evidence of ischemic heart disease in which the coronary arteriogram appears normal or near-normal. Questions as to whether a significant lesion may have been missed in the study, whether a branch was occluded at its origin and therefore invisible in contrast radiography, or whether "small vessel disease" is present sometimes remain unresolved. Publications dealing with myocardial infarction allegedly occurring without demonstrable coronary disease³ have been subjected to severe criticisms.^{4,5}

Clinical Correlations

The introduction of selective coronary cine-arteriography offered the means of showing *in vivo* a dynamic, fairly detailed view of the normal and abnormal anatomy of the coronary arterial tree, providing a more complete and reliable picture than conventional pathologic examination at necropsy, equaled only by the cumbersome and time-consuming methods of postmortem injection of coronary arteries, in conjunction with digestion of the myocardium, or ancillary roentgenographic techniques. The enthusiasm generated by the development of this technique tended to obscure the fact that the information obtained by coronary arteriography has to be

correlated with clinical manifestation of disease in a patient. Only too often is coronary arteriography presented as a broad pedestal supporting ischemic heart disease, while more properly it is but one leg of a tripod, the other two being coronary blood flow and clinical manifestations of ischemia.

Obstruction within the lumen of a coronary artery is only significant if it interferes with the flow of blood by offering resistance to flow. All other lesions should be considered potentially obstructive. Our present knowledge of coronary artery disease is not far enough advanced to know whether all such potential lesions eventually become significant obstructive lesions and, if so, how rapidly they progress. It is well known that resistance to flow occurs when the lumen of an artery is reduced by about two-thirds; such a lesion produces a pressure gradient. Obstructing plaques of this caliber present in larger branches are now of major interest in view of the feasibility of performing a surgical bypass beyond the point of obstruction. The problem may be simple: for example, an 80 percent obstructing lesion in a patient with intractable anginal pain who shows ischemic changes in an electrocardiographic stress test. However, in many patients, perhaps in the majority, such perfect clinical-anatomic correlation is absent. Given a patient with anginal pain who shows an obstructing lesion occupying 50 percent of the lumen, one can raise the following questions: Has the radiographer underestimated the degree of obstruction? Is the chest pain non-cardiac in origin? Could it be caused by ischemia in another part of the myocardium?

While proximal obstructing lesions in coronary arteries pose frequent problems in interpretation, the significance of diffuse disease of lesser branches is even more difficult to interpret as to their clinical significance. A great deal of weight is given to the finding of collateral channels filling obstructed arteries. However, if an artery appears obstructed and no collateral vessels are visible, what does it mean? Is the lesion not severe enough to produce a pressure gradient (the known stimulus for collateralization)? Is the underlying myocardium dead? Are some patients incapable of forming collateral flow, and therefore at higher risk of myocardial infarction? Or was the technique of filming not good enough to show collaterals?

The difficulties in reconciling coronary anatomy with clinical manifestations of coronary disease taught us a lesson, namely that the application of findings of coronary arteriography to the patient can usually be made only by implication. Therefore, other corroborative studies are very important. The electrocardiographic stress test is the most widely used and a valuable one. However, it also has some limitations: Patients with abnormal T-waves in the resting electrocardiogram and those taking digitalis are unsuitable for such tests. Furthermore, stress test is sometimes negative in patients with known ischemia, perhaps because of the limitation of our electrocardiographic lead system in exploring all regions of the heart. Other tests include the production of ischemia or of chest pain by atrial pacing⁶ and a hemodynamic evaluation.⁷

Benefits

Theoretically, clinical applications of coronary arteriography are almost limitless. As a method of outlining the anatomic detail of the commonest of cardiac disease, it could be used in patients with actual or potential ischemic heart disease serially, to obtain badly needed information about the natural history of coronary artery disease. However, as an invasive method, carrying an appreciable risk, it should be used only when the individual patient is likely to obtain a specific benefit from it. The primary benefit involves some action which could favorably influence the course of his disease. Occasionally, considerations other than potential therapy may justify the use of coronary arteriography, such as the investigation of atypical chest pain in younger persons.

Considerations of medical treatment do not ordinarily justify the performance of coronary arteriography. Use of our limited means of trying to alter or delay the course of coronary atherosclerosis—diet, reduction of risk factors, exercise, antilipid therapy—hardly depends upon knowledge of anatomic changes in the coronary arteries. Thus, only surgical considerations are directly related to results of coronary arteriography. The major impetus to the performance of coronary arteriography in the past five years was the availability and past popularity of the Vineberg operation, which today is largely discredited and seldom performed. The introduction of

aorto-coronary bypass operations stimulated enthusiasts to recommend wholesale performance of coronary arteriograms. Extraordinary claims are now being made regarding this operation; it is advocated as a definite means of altering the course of coronary disease or of preventing myocardial infarction; it is presented as if it were a curative operation for coronary artery disease. The operation admittedly makes good sense, its risk is reasonable, and early follow-up examinations show high patency of such bypass grafts. Thus far, no long-term follow-up examinations are available. Late closure of such bypass grafts occur—we hope infrequently, but at this time no one knows the rate of closure. Experience with ilio-femoral bypass operations indicates that at best two-thirds of grafts still are open after five years. The smaller caliber coronary vessels may have a much lower long-term patency rate. Only a totally uncritical approach to the aorto-coronary bypass operation permits the suggestion that such operations be performed prophylactically in asymptomatic or barely symptomatic patients, and that everyone recovering uneventfully from a myocardial infarction might be considered a surgical candidate. Until reliable follow-up studies are available to answer the long-range fate of bypass grafts, the operation should be reserved for patients who have disabling symptoms from coronary artery disease, preferably those in whom medical therapy is shown to be ineffective. It is unrealistic to expect such follow-up information to be available until a minimum of two to three years has elapsed.

Indications for Coronary Arteriography

After careful consideration of the ratio between the risk of coronary arteriography and the benefit to the patient, the following groups of patients can be considered reasonable candidates for the performance of coronary arteriography:

- Patients with atypical chest pain, in whom the diagnosis cannot be established in any other way may be subjected to this procedure, particularly if they are young, if the pain appears disabling, or if their occupation makes them responsible for the lives of other persons (airline pilots, bus drivers and the like).
- Patients with disabling angina, preferably of long duration and unresponsive to a good medical regimen, are the prime potential candidates

for surgical treatment and represent the largest group subjected at present to coronary arteriography.

- Patients who underwent surgical treatment may be subjected to visualization of the bypass graft or of the coronary arterial tree or both. This not only permits the evaluation of the operation, but is of benefit to the person with regard to prognosis and the possibility of further operation.

- Young persons with repeated, proven myocardial infarcts constitute a potential surgical group, even if they happen to be asymptomatic. The occurrence of two or three myocardial infarcts in short succession suggests accelerated coronary artery disease, in which operation may be justifiable even if long-range results are as yet unknown.

- Patients who are to have open heart operations and who are suspected or known to have ischemic heart disease should have coronary arteriography before the operation. The commonest conditions in this category are ventricular aneurysm and calcific aortic stenosis associated with chest pain. In some institutions all persons of "coronary age" who need cardiac operations have coronary arteriography. At present such a routine is not based upon demonstrated advantages.

Today surgical bypass operations are being done in some acute cases of coronary artery disease such as pre-infarction angina, persistent pain following acute myocardial infarction, and "pump failure"—acute or chronic—after myocardial infarction, not related to a resectable cardiac aneurysm. Such procedures are now in an experimental stage and should be limited to institutions in which every diagnostic and therapeutic step can be investigated by the most sophisticated techniques. Until an answer is available, the risk of coronary arteriography in an average laboratory does not appear justifiable.

In addition, one should mention use of arteriography at some institutions for investigation on certain clinical situations in which, in our opinion, it is unjustified from the risk-benefit standpoint. Among such situations are those of:

- Patients who have recovered from an uncomplicated acute myocardial infarction (first one), particularly those who were stricken without a preceding period of effort angina.

- Patients with effort angina easily controllable by reduction of activities or by the use of nitroglycerin or a combination of these means.

The process of the selection of patients for selective coronary arteriography can only be performed properly when the persons involved in the decision making have the complete understanding of all factors involved in the diagnostic procedure as well as in the potential surgical therapy. A regrettable cavalier attitude, stemming from excessive enthusiasm, has crept into many institutions, as some advocate that the patient's primary physician channel him directly to the person performing coronary arteriography—a radiologist or cardiac physiologist—who is then in the position of being judge and jury at the same time in deciding upon the test. Risk involved in the diagnostic procedure cannot be taken lightly. It is shown clearly that as between institutions with a full-time team performing many procedures and laboratories in which few tests are performed, there is a wide variation in risk. Often thought of as a "prestige item," an angiographic laboratory is organized in a community hospital without consideration of the necessary team approach. Coronary arteriographic films performed in institutions that do not have cardiac surgical teams available are then sent with the patient to the cardiac surgical center, where only too often the study is found to be inconclusive and has to be repeated—subjecting the patient to a double risk. One should therefore seriously question the propriety of having coronary arteriography performed in any institution other than one with a complete, active cardiac medical and surgical team. Unless proper selection procedure of patients with coronary disease is carefully followed, we falter in our duty to the patient, for it is our moral as well as legal obligation to see that the physician and the patient alike are fully aware of all factors that make up the ratio of risk to benefit.

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Dermatologic Radiotherapy—R.I.P.

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■ *A questionnaire returned by nearly 3,000 dermatologists indicates that about 75 percent of them have discontinued completely the use of x-ray therapy in acne. An additional 11 percent use it in less than 10 percent of their patients who have this disease.*

"Hazards" constituted the greatest deterrent to the use of ionizing radiation. Yet the assumption that it can cause skin cancers, in the absence of radiodermatitis, is not proved and its importance as an additive energy to solar radiation is considered to be limited.

About one-third of the respondents expressed belief that better treatments were available for this condition. An equal number were concerned with public resistance to this therapeutic agent, which, however, seems to be more apparent than real. Probably the major roadblock was posed by the dermatologic training centers where teaching was withheld despite a rule of the American Board of Dermatology favoring it. Other factors mentioned with some frequency included ineffectiveness of radiotherapy, lack of equipment, and fiscal and medicolegal considerations.

This study indicates that dermatologic radiation therapy is passing into oblivion.

AS A PERPLEXING SPIN-OFF of the age of the fissioned atom, the dangers of x-radiation came to be so celebrated that use of this helpful energy in the treatment of acne has sharply diminished.

To find out how much and for what reasons its use for this purpose has been curtailed by specialists in a field where once it was widely employed, a simple questionnaire was sent to 4,280 dermatologists in the United States, Canada and in the Caribbean. Thirty-four were

returned by the postoffice as being undeliverable, leaving a total of 4,246 that presumably reached the addressees. A total of 2,871 (67.6 percent) were returned. This is significant both from the standpoint of total number and of percentage received.

Results

The returns were subjected to computer analysis. It was obvious from this survey, that dermatologic radiotherapy is a thing of the past: 75 percent of the respondents never use x-ray therapy in acne and an additional 11.1 percent use it in less than 10 percent of the patients. The incidence of complete avoidance varied in dif-

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ferent age groups—97.8 percent of those not yet in practice, 90.4 percent of those in practice one to five years, 82.9 percent in practice, 6 to 10 years, 70 percent 11 to 20 years and only 57.4 percent more than 20 years. Since the newest practitioners use it least, the proportion of physicians employing this energy in the management of this dermatosis can be expected to decrease as time passes.

One must wonder about the reasoning behind this discarding of x-radiation in this condition. The respondents were asked to mark boxes explaining why they discontinued use of this therapeutic agent. The results are interesting. The statistics do not add up to 100 percent because some of the physicians did not check any boxes while others marked more than one. Incidentally, there was a place for "comments," and 120 respondents took advantage of this to berate the use of x-radiation in benign dermatosis in terms such as "criminal," "no place in dermatology," and "the lack of teaching of this is commendable." Of some interest is the fact that 98 of those who answered took the time to jot down good things about it, including "the best treatment for acne," "my Sunday punch in resistant cases," and "I gave up x-ray therapy but recently have returned to it because of disillusionment with other therapeutic approaches." So while the respondents were vehement in their evaluation of this approach, there were about as many on one side of the fence as on the other.

But to consider what reasons were given for discarding roentgen rays in dermatology, the following findings resulted.

Hazards. This was the number one deterrent. It was mentioned by 1071 of the group (37.3 percent). Yet, there is adequate evidence that dermatotherapy does not cause shortening of life, leukemia, radiodermatitis or genetic mutations, and in fact no one mentioned any of these factors specifically. Most stuck to the general term *hazards*.

However, a number, especially among the less experienced age groups, pointed out that they have encountered patients with basal-cell epitheliomas who had had x-ray therapy for acne many years previously. They seemed to consider this significant. On the other hand, it has been demonstrated repeatedly that small doses of radiation do not cause premalignant or malignant alterations.^{1,2} It is a question of overdosage.

While the possibility of co-carcinogens is recognized, there is no evidence that a course of 600 to 900 r of superficial x-ray therapy given in 10 to 12 divided doses contributes more to potential solar carcinogenesis than does a round of golf or an afternoon of swimming.

Better Treatments. A total of 875 respondents (30.4 percent) expressed belief that x-ray therapy was unnecessary since there were better alternate treatments available. Antibiotics, especially tetracycline, were easily the most popular agents mentioned. However, actinotherapy, cryotherapy, local remedies, acne surgery, corticosteroids, anticontraceptive tablets, and others, had their adherents. This acceptance did not vary significantly in the various age groups.

My own results with all of these methods *plus* radiotherapy is not so good that I can not use all the help that I can get in the management of my patients with acne. The use of tetracycline does not contraindicate the incorporation of additional measures into the regime, including x-radiation. The results of x-ray treatment can be improved by the addition of antibiotics. There is no evidence that either should be used alone. The therapeutic results are imperfect with each. Failures are not uncommon. In a study (being published elsewhere) of 1,051 patients with acne treated with x-radiation, 147 had complete clearing and more than 500 had improvement that was estimated at over 85 percent. This investigation indicates that x-radiation is of benefit in the management of this dermatosis and should not be discarded.

Public Resistance. The importance of this facet can be gauged by the realization that 32.2 percent of the respondents mentioned this as a factor in their avoidance of radiotherapy. It is of interest that this assumed increasing importance with greater experience. Public resistance to the use of x-rays concerned only 9.8 percent of those not in practice, 18.2 percent of the one to five year group, 30.0 percent of the six to 10 year group, 40.4 percent of those with 11 to 20 years' experience and 50.9 percent of those who had been treating dermatologic patients for more than 20 years.

Of course we have all encountered the patient (often an educated intellectual) who questions the safety of this treatment or refuses it. Since the squeaking wheel gets the grease, we tend to overemphasize his complaint. The actual effect

of this was studied in the previously mentioned survey of 1,051 patients treated with x-rays for acne. It was found in that investigation that 50.5 percent completed the 12 treatments recommended. Approximately 80 percent of the group received more than six treatments. Only 2.8 percent did not return after the first treatment. The years of greatest resistance to this modality are said to have been 1946 to 1960, a period which embraced 52.4 percent of the patients in the survey. Of this group, 62.2 percent accepted treatment with ionizing radiation compared with 59.1 percent for the entire series seen between 1937 and 1969. Actually, a greater proportion of patients completed the course of treatment during this time (52.6 percent against 50.5 percent) and more submitted to over six treatments (82.4 percent against 79.5 percent) than for the entire group. In other words, resistance to this energy was actually less during the so-called "scare period."

Lack of Training. The American Board of Dermatology, Inc., publishes a Guide for Residency Programs in Dermatology. This says: "The resident should be prepared to undertake the radiobiologic therapy of skin lesions when indicated. He should have had practical clinical instruction in radiologic techniques, as well as study of the underlying basic principles. Special attention should be devoted to the practical aspects of radiation protection. He should be aware of the clinical significance of the newer radiologic tools, including isotopes."

It does sound clear, then, that the training centers are charged with the responsibility of providing the trainee with practical information on this subject. Yet, according to Cipollaro,³ none of these institutions offers a formal course in this modality. Repeatedly, in answers to the questionnaires, we find the response, "We were not taught how to use x-rays." Three hundred and ninety-one (13.6 percent) of the entire group explained (at least partially) their avoidance by this factor. This decreased with increasing years in practice (44.7 percent in those who had not yet entered practice, 36.4 percent in the group with one to five years' experience, 19.0 percent in the six to ten year group, 7.8 percent in the 11 to 20 year bracket and 5.2 percent in those trained more than 20 years ago). The lesson is clear: The training centers, with or without good reason, are preventing the new

dermatologist from acquiring the requisite skill in x-ray therapy of those trained more than 20 years ago. This is the most potent factor in the reduced use of this dermatologic tool. As one experienced dermatologist pointed out, it is a good thing that dermatoradiotherapy is dying out because the "new dermatologists know nothing about its use and their adoption of this modality would lead to great damage."

Ineffectiveness. Three hundred and forty-two correspondents (11.9 percent of the series) felt that x-ray therapy was a poor therapeutic method for acne. The main complaint was concerned with recurrences. While one cannot minimize the truth of this allegation, previous investigations have indicated that this can be minimized by withholding x-ray therapy until the patient attains the age of 18 years or more. Since the disease is self-limited and tends to disappear in many cases in the late teens and early twenties, the recurrence rate is lower in older ages than when the energy is applied to individuals in their midteens. A few practitioners are using more x-ray therapy than previously. Some of the reasons for this swimming against the current might be compared with the reasons for discarding the use of the modality. "Therapeutic efficacy" was mentioned by 115, "disappointment with other methods" was mentioned by 73, "safety" by 33, and "other reasons" by 19. In other words, not all dermatologists condemn its use.

Lack of Equipment. While this factor could have been overcome easily had there been the will to do so, 333 respondents (11.5 percent) mentioned this as a problem. A number did not feel that they wished to have the equipment. Two experienced dermatologists offered to donate their machines without charge to anyone who would take them away. One said that the clinic in which he works offered to buy him apparatus for radiologic therapy but he refused because of "therapeutic ineffectiveness." Predictably, this factor was more important in the younger age groups because in the "old days" all dermatologists purchased a source of x-rays on entering practice. The range of those mentioning the "lack of equipment" varied from 29.2 percent in the one to five year group to 4.3 percent among those in practice more than 20 years. On the whole, this is not an important cause for not using radiotherapy in acne.

Fiscal Considerations. The cost of supplying x-radiation therapy in the dermatologist's office is not inconsiderable. I have a 120KV superficial therapy machine plus grenz rays equipment. They cost approximately \$6500. About 25 percent of my office space, hence one-quarter of my office rent, goes to the housing of these machines. In addition, I pay personal property taxes to the city and county plus an annual x-ray tax to the state. My malpractice insurance rate is nearly doubled because I use this modality, even though the insurance company admits it cannot recall any litigation stemming from x-ray therapy of acne.⁴ Many practitioners wonder if the therapeutic results obtained warrant the purchase and use of an ionizing radiation installation. Many fear the threat of increased probability of medicolegal complications. Most practitioners do not charge extra for such therapy, including it in the office-visit charge.

Sixteen physicians felt that the few cases of acne they would treat with x-ray did not justify the cost of buying and using the equipment. Forty-five said that they avoided this modality because of increased expense of malpractice insurance and because of fear of medicolegal entanglements.

Discussion

In considering the results of this questionnaire, one must realize that it established only what the thinking is among dermatologists in the United States, Canada and the Caribbean Islands today. Obviously, the use of x-ray therapy in acne has decreased almost to the point of ex-

inction. The reasons for this are multiple in the minds of those who avoid this energy. Previous studies have demonstrated that many of the explanations advanced—hazards, therapeutic inefficiency and public resistance—are more apparent than real. The theory that by additive effect ionizing and solar radiation can cause cutaneous malignant disease is inviting but unproven and probably a rationalization. Nor is it established that small doses of x-radiation are carcinogenic to the skin, thyroid gland or other portions of the anatomy.

Why, then, the obvious decrease in its use? It is believed that there are two potent factors involved. Most important is the lack of teaching in this field, and second is scare propaganda.

An obvious factor overlooked by about 99 percent of the correspondents is that x-ray is an adjunct, not a complete treatment for acne. There is no question that tetracycline is the number one accepted therapeutic agent in this disease, but the point is, there is no reason why x-ray therapy if proven safe and effective—which I believe it has been—could not be given concurrently with antibiotics and local remedies. If it were not for the roadblocks of "no training" and "scare propaganda," x-ray therapy could still be an important factor in our management of this troublesome dermatosis.

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A FEW NASAL EOSINOPHILS DO NOT AN ALLERGY MAKE

We've been trained to believe that eosinophils in the nasal smear always suggest some allergic condition. However, I'm only concerned with eosinophils when I find them in large numbers. If they are there in over 30 percent, 40, 50, 70, or 100 percent, then we're dealing with a hyperallergic state. I think it's hard to apply significance to the presence of 5, 6, 7, or 10 percent eosinophils; they vary from one time of day to another. So I don't think one should overemphasize the finding of a small number of eosinophils.

—JOSEPH L. GOLDMAN, M.D., New York City
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Orthopedic Rehabilitation of the Stroke Patient

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■ *Rehabilitation of hemiplegic patients begins with setting reasonable functional goals and a treatment plan to reach them. During the initial illness an effort is made to begin range of motion exercising and positioning to prevent contractures. Transfer from bed to chair is recommended as soon as the patient's general condition permits.*

Upper extremity function depends on sensory and motor function as well as visual and central cerebral impairment. Spastic symptomatic contracture of the shoulder must be prevented by adequate orthopedic management of any musculoskeletal problems such as arthritis or tendinitis and the initiation of an active exercise program. Surgical release of contractures is occasionally indicated in refractory cases. Elbow flexion and pronation flexion deformity of the forearm and hand have also required surgical release on occasion.

The goal of lower extremity function is ambulation. A double up-right short leg brace aids stability in gait. Long leg braces are not used but a cane may be necessary for balance assistance. Contractures must be prevented by an exercise program or surgically released.

PATIENTS SUFFERING WITH HEMIPLEGIA secondary to cerebrovascular accident are being seen in increasing numbers at rehabilitation centers and private facilities. Realistic goals for function and programs of treatment may not be familiar to physicians whose conventional training has been oriented toward treating acute illness. In a modern rehabilitation center, treatment is carried out by a team composed of physicians, therapists,

psychologists, nurses, and social workers. There are too few of these comprehensive centers. The purpose of this article is to describe functional goals and a reasonable plan of treatment that can be offered to hemiplegic patients by a family physician and an orthopedist. The material presented is based on experience gained on the Stroke Service at Rancho Los Amigos Hospital over the last five years.

Rehabilitation should commence immediately after the occurrence of the cerebrovascular accident. It falls into two distinct phases. The initial phase begins during the period of acute illness, the second phase when the neurological

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Figure 1.—The reciprocal pulley exerciser permits patient to initiate and maintain an exercise program. The exercise regimen shown has proved valuable in the management of the contracted shoulder in the stroke patient.

hemiplegic state has been stabilized, usually about three months after the acute attack. The second stage requires a good prognosis, adequate orientation to comprehend instructions, ability to communicate, and motivation.

Initial Phase

Every effort is made to prevent flexion contractures by appropriate positioning of the patient. Rolled sheets or padding are used in the bed to prevent plantar flexion of the ankle, abnormal rotation of the hip, adduction and internal rotation of the shoulder, and an imbalanced position of the hand. The patient should be turned from back to side, as tolerated, and should also be turned into a prone position when medically acceptable to prevent hip flexion contractures. This early splinting program should be managed by regular duty nurses who are acquainted with the problems of flexion contrac-

tures and the importance of preventing pressure sores. Once a pressure sore has occurred, rehabilitation is greatly delayed. Nursing rounds should routinely include putting the patient's extremities through a range of motion several times during the day.

The patient should be taught to exercise his own extremities as soon as possible and how to use the equipment available for that purpose (Figure 1). This has the dual function of maintaining range of motion and of initiating the idea that the patient must now begin to help himself. As soon as his general condition allows, the patient should begin to transfer from bed to wheelchair. Becoming upright in a chair gives the patient a boost in morale that enables him to continue his efforts to regain independent status. It also starts an increased flow of sensory input to the central nervous system. Transfers from bed to chair require practice and assistance. The chair is rolled to the unaffected side so that the patient may use his good hand and normal peripheral vision to perform the transfer. When seated in the chair, the patient is examined for balance and support of the affected arm. An outrigger sling holding the shoulder moderately abducted has proved useful in the prevention of symptomatic adducted shoulder contractures (Figure 2).

Definitive Phase

The Upper Extremity

Major factors of impairment of the upper extremity include sensory loss, spasticity and poor motor control, occurrence of flexion contractures, and impairment of body image.

Serious sensory impairment is seen in more than half of patients with affected upper extremities. Many of these patients have adequate sensation in the shoulder, elbow and forearm, but lack position sense or discrete object identification in the hands. If a patient still shows major impairment in sensation three months after onset of hemiplegia, it is likely that the sensory defect will be permanent. No matter how much motor function the patient has in the affected hand, lack of sensation will almost invariably result in his becoming one-handed. Major treatment efforts should be directed toward making the best use of the functioning hand for the self-care and other activities of daily living rather than waste time and effort trying to teach skills that cannot be mastered with the involved hand.



Figure 2.—The outrigger sling is used to dynamically balance the weight of the arm and also allow for some maintenance of shoulder abduction in the treatment of stroke patient.

Every effort should be made to prevent painful limitation of motion in the joints of the affected extremity. Shoulder pain and restricted range of motion have been a particularly difficult problem in stroke patients. A daily program of ranging should be begun immediately. Use of reciprocal pulleys so that the good arm can help exercise the affected upper extremity has proved of value (Figure 1). The cause of shoulder pain should be sought—bursitis, tendonitis, acromioclavicular joint arthritis, or perhaps a too enthusiastic exercise program in the presence of internal rotator spasticity, primarily in the subscapularis muscle.

If despite a therapy program the patient continues to complain of shoulder pain and demonstrates increasing spasticity in the internal rotator group, associated with decreasing range of motion, surgical intervention should be considered. Operation is contraindicated when a post-operative program is not available to the

patient. One must beware of diffuse pain affecting the entire hemiplegic side that is not amenable to any form of surgical therapy. Where there is spasticity in the internal rotator muscles, relief of pain and increased range of motion have been obtained following resection of about one inch of the musculotendinous junction of the subscapularis muscle where it overlies the anterior capsule of the shoulder joint.¹

Flexion of the elbow may become a serious problem and ultimately lead to a flexion contracture. Standing and walking usually accentuate the elbow flexion. Patients occasionally will request treatment of this contracted posture in order to improve their appearance and balance during walking. Reduction of elbow flexion can be achieved by injecting 3 percent phenol into the musculocutaneous nerve. Relief following this procedure may be temporary, however, and in some cases spasticity has returned after about six months. Elbow flexion also can be reduced by transecting the brachialis muscle or elongating the tendinous insertions of the biceps and brachialis muscles.

In association with elbow flexion, pronation of the forearm and acute flexion of the wrist and fingers frequently are seen in hemiplegic patients. Daily range-of-motion exercising should be undertaken to prevent contractures that will restrict hand function. Tight flexion of the fingers may cause pressure necrosis of the skin of the palm. Splints made from either metal or molded plastics frequently are used to maintain normal position of the wrist and fingers when there is only slight spasticity. When a patient is progressively becoming worse or has reached a functional plateau that is unacceptable because he cannot get the fingers out of the palm of his hand or his wrist out of an attitude of extreme flexion, operation may be considered. Three percent phenol injected by open operation into the median motor nerves will produce reduction of spasticity over a period of about six months.² This injection is used where the neurological status is changing and the orthopedist chooses to defer definitive operation.

Release of the flexor muscle origin or selective tendon lengthening procedures may improve appearance or correct contractures that limit patient hygiene. In such cases it is important to stress to the patient and his family that true functional improvement is not anticipated fol-

lowing the operation. Where there is good sensation in the forearm and hand and some evidence of selective motion underlying the acute flexion of the wrist and fingers, it is reasonable to expect improved function with flexor release.³

The Lower Extremity

The most common abnormality seen in the hemiplegic patient following a cerebrovascular accident is an equinovarus deformity of the ankle during the swing phase of gait. This inverted and plantar flexed attitude of the foot and ankle usually is due to spasticity in the calf muscle and an imbalance of the muscles on the dorsum of the foot (the inverters overpowering the evertors). If this imbalance is untreated, the patient may fall when attempting to walk, and restrict his activity to the wheelchair. If the muscle spasticity is of moderate severity, it usually can be corrected by using a short leg brace. Our experience at Rancho Amigo has been that a double upright brace with a limited range ankle joint is more effective in controlling spasticity and excessive pattern responses than a spring brace, which stretches the calf muscles and therefore enhances the spasticity.

In addition to controlling the equinovarus deformity, the double upright brace with the limited range ankle joint also controls ankle instability when the muscles about the ankle joint are weak (Figure 3). Proprioception impairment is another problem of the hemiplegic patient, and knowledge that the foot is in a stable neutral position greatly assists in foot placement.

Another feature of the hemiplegic is instability of the knee. Instability in either hyperextension or flexion is caused by imbalance between quadriceps and hamstrings. The double upright brace with a locked ankle joint controls the tibia and produces knee stability, which increases the ability of the patient to walk (Figure 3). When calf spasticity is severe, a double upright short leg brace is not capable of controlling the situation. Surgical intervention is indicated in such cases. Calf spasticity and plantar flexion are corrected by lengthening the Achilles tendon or by resecting the distal one-third of the soleus muscle. The imbalance between inversion and eversion of the foot is corrected by splitting the tibialis anterior tendon and transferring the lateral half into the lateral aspect of the dorsum of the foot. It has been our experience that flexion contracture of



Figure 3.—The double upright brace with limited or fixed ankle provides support and proprioceptive cues for hemiplegic patients and thus assists ambulation.

the toes becomes a problem following such operations and therefore we simultaneously transfer the toe flexors into the toe extensors during the same procedure. In our experience there is never indication for a long leg brace; knee and hip flexion contractures are corrected by muscle releases. Prevention of contractures is better than treatment and is best achieved by stimulation of antagonist muscles, appropriate range of motion, and stretching of joints by appropriate positioning.

Self Care

The aim of the rehabilitation program for hemiplegic patients is to allow them to achieve as much independence as is possible considering the degree of functional impairment. Patients must be evaluated for their ability to learn new skills and participate in treatment programs. This may involve psychological testing, careful evaluation of visual fields, and an analysis of the

patient's ability to communicate through gestures and speech. A program that is unrealistic as measured against the patient's capacity for recovery only frustrates the patient and disappoints the family. It therefore is essential that realistic goals be set before treatment commences. The patient must be encouraged to be as independent as possible. Also the family must be instructed in assisting him to utilize his self-care skills rather than depend on others. Special equipment, such as one-armed knives and long-handled bath sponges, are of great assistance and should be ordered as soon as possible. Discussion with the family will make apparent the need for structural alterations in the patient's home, such as the addition of ramps for wheelchair use and grab-rails by the sides of toilet and bath, and alteration of bed position so the patient can get in from his unaffected side. Such alterations

should be made as soon as possible so that the patient can fit readily into his home environment.

An orthopedic program oriented toward prevention of contractures, ambulation, and maximal use of the unaffected side can be combined with a general medical and environmental adaptation program to permit the patient to rejoin society on the best possible terms. This is the goal of the orthopedic rehabilitation of the stroke patient and is best achieved by means of a multispecialty team approach.

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PLACING THE NASOTRACHEAL TUBE

To insure proper placement of the tube in blind nasotracheal intubation, I advise use of a technique of external visualization. Do not try to listen to the tube while you are aiming to get it in. Rather observe the patient's neck. Stand up and look at the neck as you advance the tube. You will find that wherever the point of the tube goes, you will be able to see its location from the outside. If it gets right into the trachea and it moves on down, you will see a little ridge move down along the midline as the point of the tube is touching the anterior wall of the trachea. If it does not enter the trachea, you will see a little shadow wherever the point of the tube is. It will be in one or two of the lateral walls of the pharynx; it may be hung up in front of the epiglottis; or it may enter the esophagus. If it's in the esophagus, you extend the head a little bit and that will bring the point of the tube up. If it's in front of the epiglottis, you flex the head a little and hold the mandible forward to get the epiglottis out of the way. If it's to one side or the other, you turn the tube so it will go in the direction you're after. With another gentle tap, the tube has been redirected and it will enter the trachea.

—JAY JACOBY, M.D., Philadelphia
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Transmission of Rubella Vaccine Virus From Vaccinees to Contacts

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■ *The report presents evidence of the transmission of HPV-77 derived rubella vaccine virus from vaccinees to two susceptible contacts. The first instance of transmission was to a child who served as a transmission control on a "closed" study ward, and the second was to an antibody-negative mother in an "open" family study. Neither of these persons had any clinical evidence of rubella. Both had significant increases in rubella hemagglutination inhibiting (HAI) antibody titers, but detectable complement fixing (CF) antibodies did not develop in either. With the kind of antigen used in our rubella CF test, this pattern of serologic response is characteristic of, but not diagnostic of, infection with the rubella vaccine virus.*

The serological evidence which was compatible with rubella vaccine virus infection, the complete absence of serologic or clinical evidence of "wild" rubella virus infections among the other four rubella susceptible transmission control children and the security precautions employed to ensure isolation on the "closed" ward, make "wild" rubella virus infection extremely unlikely.

The evidence for rubella vaccine virus infection in the other susceptible contact is not as conclusive, because "wild" rubella virus infection is difficult to rule out in any person living in an "open" family situation. Nevertheless the need for more data is emphasized by the virtual certainty that rubella vaccine virus transmission did occur in the subject on the isolation ward, plus the high probability that the infection observed in the family group setting also represented transmission of rubella vaccine virus. Such data can only come from close surveillance of recipients of live rubella virus vaccines and their contacts in the future.

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IN THE COURSE OF evaluating several HPV-77 derived live rubella vaccines utilizing "closed" and "open" population groups, there were several findings of potential clinical and epidemiological significance. Some of these data have already been reported, including mention of the probable transmission of a rubella vaccine virus from a vaccinee to a susceptible contact in a closed pop-

ulation.¹ Other experiments, still unpublished, disclosed a second instance of probable rubella vaccine virus transmission to a susceptible contact. These two instances of probable transmission of rubella vaccine virus from vaccinees to susceptible contacts are sufficiently unusual and potentially important to warrant reporting in detail. Therefore, the design of the studies, the relevant clinical and laboratory findings and the significance of transmission of rubella vaccine virus from vaccinees to contacts will be discussed.

Methods of Procedure— “Closed” Population Study

Vaccine study groups. The susceptible contact who had evidence of spread of rubella vaccine virus from a vaccinee belonged to Group 4 of six groups of children studied at Pacific State Hospital, Pomona, California. After appropriate parental consents, members of all six study groups were observed for serologic responses to HPV-77 and HPV-77 derived live rubella vaccines and for evidence of spread of vaccine virus from vaccinees to susceptible contacts. In all, the study groups consisted of 46 vaccinees and 36 susceptible contacts. Groups 1 to 3 each had 8 vaccinees and seven contacts, Group 4 had ten vaccinees and five contacts, Group 5 had seven vaccinees and seven contacts, and Group 6 had five vaccinees and three contacts.

As all the six groups were housed in the same ward and the experimental design was similar, only the experiment with Group 4 will be described in detail. Study Group 4 consisted of 15 rubella-susceptible* mentally retarded children selected from the population of the Pacific State Hospital, Pomona, California. Ten of the 15 subjects, taken at random, received live rubella virus vaccine, and the remaining five served as sentinels, or transmission controls, to detect any vaccine virus spread. The ten vaccinees (six boys and four girls) ranged in age from 39 months to 91 months with a median age of 73.5 months. The cause of the mental retardation in nine of the vaccine recipients was said to be “nonspecific encephalopathy,” and the tenth had Down’s syndrome. The transmission controls (four boys and one girl) ranged in age from 46 months to 107 months with a median age of 58 months. The cause of the mental retardation in all five trans-

mission controls was “nonspecific encephalopathy.” All 15 subjects, the ten vaccinees and the five susceptible contacts, were ambulatory.

Study facility for closed population groups. Subjects were admitted to a special 15-bed ward at Pacific State Hospital, where clinical and virologic surveillance could be maintained under controlled conditions. The study ward was designed to accommodate groups of 15 subjects under isolated conditions to prevent the accidental introduction of “wild” rubella virus before and after either administration of live rubella virus vaccines or upon later readmission of such subjects for challenge by exposure to natural rubella or by the intranasal administration of low passage rubella virus. The ward was locked; ingress and egress were strictly controlled; each study group had no contact with any other patients, regardless of age, during the pertinent observation periods. The isolation ward had separate eating and play facilities including an outdoor play-yard surrounded by a wooden fence. Staff personnel or adult visitors were allowed on the study ward only if previous tests had shown that they possessed both neutralizing and HAI antibodies against rubella virus.

Vaccine used. The HPV-80 live rubella virus vaccine was derived from the original HPV-77 vaccine and was produced in African Green Monkey Kidney (AGMK) tissue culture. The HPV-80 vaccine was produced and supplied to us by the Eli Lilly Company, Indianapolis. Each vaccine recipient received 0.5 ml of vaccine injected subcutaneously. The potency of the vaccine was assayed by titration in AGMK tissue culture in our laboratory, and each 0.5 ml dose was found to contain $10^{3.0}$ interfering dose_{50's} (ID_{50's}) per ml.

Vaccine administration and clinical surveillance. As was noted above, each of the ten vaccinees in Study Group 4 received HPV-80 live rubella virus vaccine subcutaneously in a volume of 0.5 ml. No placebo injections were given to the five susceptible contacts who served as transmission controls. All 15 of the children remained on the study ward for 63 days. During the first 30 days, they were examined daily by a physician for clinical signs of rubella; during the remaining 33 days, they were watched closely by the ward nursing personnel, who called a physician if signs of any illness were observed. During the entire 63-day period, the ten vaccinees and the five transmission controls were allowed to mingle

*Rubella hemagglutination inhibiting (HAI) antibody titer of less than 1:8.

freely during meal times, at play on the ward, and at play in the enclosed play-yard.

Virus isolation and serological studies. Post-immunization patterns of pharyngeal excretion of rubella vaccine virus had seemed well established by earlier studies of other investigators²⁻⁴ and by the first three groups of children studied by us at Pacific State Hospital.¹ Furthermore, there had been no previous observations of rubella vaccine virus spread to susceptible contacts of vaccinees.²⁻⁴ Consequently, the protocol for the virologic surveillance of the subjects in study Group 4 was not optimally designed to provide confirmation, by virus isolation, of any spread of rubella vaccine virus to the susceptible contacts. Throat swabs for virus isolation attempts were collected only once from all 15 subjects in the study group. The swabs were taken immediately before injection of vaccine into the ten vaccinees. Heparinized blood specimens were collected on a regular schedule from vaccinees, but not contacts, and tested in an attempt to detect viremia.¹ The rubella virus isolation and identification procedures described by Parkman et al⁵ were employed and, as was reported earlier, viremia was detected in two of the vaccinees.¹

Serum specimens for antibody determinations were collected from all 15 subjects on the day before vaccine administration and on days 30, 60, 90, 120, and 180 after vaccine administration. After kaolin absorption to remove nonspecific inhibitors, these serum samples were tested by microtiter techniques for rubella HAI and CF antibodies.⁶⁻⁸ Serial serum specimens from each subject were titrated in the same "run" to allow more precise detection of significant increases and decreases in antibody titers. Control sera with known rubella HAI and CF antibody titers were included in each "run" as a quality control measure, and all tests were repeated at least once to check the reproducibility of results. Using an antigen derived from "packed cell" preparations of infected BHK-21 tissue cultures,⁹ we have never detected CF antibodies in an isolated vaccinee, although CF antibodies frequently develop in response to natural rubella virus infection.¹

Methods of Procedure— "Open" Population

Vaccine recipients. The subjects were recruited from families who were subscribers to the

Southern California Permanente Medical Group, Panorama City, California. The ideal family group included at least two rubella-susceptible children. Susceptible children and susceptible fathers were considered eligible to receive live rubella virus vaccine. Families with susceptible mothers were included, but none of the mothers was given either the vaccine or the placebo.

Vaccine used. The subjects received the HPV-77, DK-12, live rubella virus vaccine, produced in primary canine renal cells. The vaccine was manufactured by Philips Roxane Laboratories, Inc., Columbus, Ohio, and supplied to us for our studies. Each vaccinee received a dose of 0.5 ml of vaccine subcutaneously. The potency of the vaccine was assayed by titration in primary AGMK tissue culture in our laboratory. It contained $10^{3.5}$ MD_{50} 's per 0.5 ml.

Vaccine administration and clinical surveillance. Before entry into the study, each member of every volunteer family had his serum screened for the presence of rubella HAI antibodies. All families who participated in this study had at least two family members, other than the mother, who were able to serve as vaccinee and transmission control.

On the day vaccine was administered, each subject had another serum specimen drawn for later use in determining antibody titers before vaccination. Then half of the susceptible participating children, taken at random, in each family received rubella virus vaccine, and the other susceptible children received a placebo injection of 0.5 ml of normal saline solution. All susceptible fathers received rubella vaccine on day 0. None of the susceptible children nor their parents knew whether they had received placebo or vaccine. Thirty days following their initial inoculation, all family members, whether vaccine or placebo recipients, returned. At this time, blood was drawn again for later rubella antibody determinations. Children who had received the placebo were given vaccine and children who previously received vaccine were given the placebo. The fathers did not receive further injections of any kind. Every subject was to return 30 days later for the collection of another blood specimen. Subjects in whom antibodies did not develop by day 30 after vaccine administration, had specimens drawn again 30 days later.

Clinical surveillance following either vaccine or placebo administration was maintained for a

period of 60 days for each susceptible subject (children and fathers) who entered the study. A check-off type of daily symptom diary, kept by each mother for her entire family, was utilized for surveillance. Among the symptoms listed were the presence or absence of rash, arthritis, adenopathy, symptoms of respiratory disease and fever. The parents in each family were instructed in the use of clinical thermometers and were told to record the temperature of each participant once a day. If necessary, clinical thermometers were provided for each study participant. Further, the parents were instructed to call a member of the research team if any symptoms of illness appeared. Each diary was reviewed with a parent at the end of 60 days.

Virus laboratory studies. No virus isolation studies were performed on any of the study subjects, regardless of whether they had received vaccine or placebo.

Sera were collected from all susceptible children and participating fathers on day 0 (the day of initial administration of vaccine or placebo) and on days 30 and 60, and again, if necessary, on day 90. Serum specimens were collected from all the mothers immediately before and again 60 days after the first introduction of vaccine into the family. It should be re-emphasized that none of the mothers received any injection—neither live rubella virus vaccine nor placebo. Whenever possible, sera from any immune children and immune fathers were also collected on day 0 and again 60 days after the introduction of the vaccine into the family.

Rubella HAI antibody titrations were performed as described for the “closed” population, with one difference: nonspecific inhibitors of hemagglutination were removed by the $MnCl_2$ -Heparin technique¹⁰ instead of kaolin. The CF antibody titrations were performed by the same antigen and techniques described for the “closed” population.

Results

Closed population, frequency of transmission of rubella vaccine virus from vaccinees to susceptible contacts. Among six study groups, there were 46 subjects who received HPV-77 or HPV-77 derived vaccines and 36 susceptible contacts who served as sentinels for the detection of any vaccine virus transmission. Only one contact had

laboratory evidence of vaccine virus spread, an overall frequency of 1 in 36, or 2.8 percent. As that contact subject belonged to Study Group 4, the sequence of events in that group will be discussed in detail.

Closed population, serological responses among Study Group 4. As noted in Table 1, seven of the 10 HPV-80 vaccinees had significant increases in rubella HAI antibody within 30 days after inoculation. Three of the vaccinees failed to develop detectable rubella HAI antibody, and none of the ten developed detectable rubella CF antibody. Table 1 also shows the sequence of serological responses of the only one of the five susceptible transmission controls (Subject 7101) who had a significant increase in rubella HAI antibody. It can be seen that the pattern of antibody responses displayed by Subject 7101 resembled that characteristic of the vaccine virus infection rather than infection induced by a “wild” rubella virus, in that an HAI antibody titer rise occurred without a CF antibody response. Furthermore, the HAI antibody titer rise in Subject 7101 occurred between day 30 and day 60, a time sequence compatible with his acquisition of infection from one of the vaccinees. Neutralizing antibodies to rubella virus also appeared between days 30 and 60 in Subject 7101 (Table 1), but the increase in titer from less than 1:2 to 1:2 cannot be considered significant.

Closed population group, virus isolation studies and clinical surveillance. None of the single pharyngeal swabs obtained on day 0 from each of the ten vaccinees and each of the five transmission controls yielded rubella virus. Rubella virus was isolated from whole blood specimens obtained from Vaccinee 7111 on days 12 and 13 (Table 1). Vaccinee 7114 yielded rubella virus from whole blood specimens on days 11 and 12 and from plasma on day 11.

None of the ten vaccinees nor five transmission controls had illnesses resembling rubella during 63 days of isolation and observation following administration of vaccine to the ten vaccinees.

Open population studies, vaccine recipients. Among the 124 families who volunteered to participate in the study, 109 had two or more rubella-susceptible children, thereby qualifying for inclusion. It proved possible to collect complete clinical and serological data on 75 families. The family included the mother and father as well as two children, aged one year and seven months

TABLE 1.—*Serological Responses Following the Administration of HPV-80 Rubella Vaccine Among Vaccinees and a Susceptible Transmission Control*

Vaccinees	Antibody types	Days post HPV-80 inoculation						
		0	15	30	60	90	120	180
7103	HAI	<8	<8	<8	<8	<8	<8	<8
	CF	<8	<8	<8	<8	<8	<8	<8
7105	HAI	<8	<8	<8	<8	<8	<8	<8
	CF	<8	<8	<8	<8	<8	<8	<8
7107	HAI	<8	<8	<8	<8	<8	<8	<8
	CF	<8	<8	<8	<8	<8	<8	<8
7100	HAI	<8	8	≥ 1024	512	512	256	256
	CF	<8	<8	<8	<8	<8	<8	ND*
7108	HAI	<8	<8	128	256	256	256	256
	CF	<8	<8	<8	<8	<8	<8	<8
7109	HAI	<8	<8	128	128	128	128	32
	CF	<8	<8	<8	<8	<8	<8	<8
7111†	HAI	<8	<8	64	64	64	64	64
	CF	<8	<8	<8	<8	<8	<8	<8
7112	HAI	<8	<8	64	64	64	64	64
	CF	<8	<8	<8	<8	<8	<8	<8
7113	HAI	<8	<8	64	256	256	512	512
	CF	<8	<8	<8	<8	<8	<8	<8
7114**	HAI	<8	<8	256	256	128	64	128
	CF	<8	<8	<8	<8	<8	<8	<8
<i>Transmission Control</i>								
7101	HAI	<8	<8	<8	128	256	128	256
	CF	<8	<8	<8	<8	<8	<8	<8
	Neut‡	<2	<2	<2	2	ND	ND	ND

* Not done

† Blood isolate on days 12 and 13

** Blood isolate on days 11 and 12, plasma isolate on day 11

‡ Neutralizing antibody

and three years and 11 months. All family members had rubella HAI and CF antibody titers of less than 1:8 at the onset of the study (Table 2). On March 15, 1969, the older child and his father received HPV-77, DK-12, live rubella virus vaccine and the younger child, a daughter, received a saline placebo. The mother did not receive any injection—neither vaccine nor placebo. The family was unable to return for their scheduled appointment for rebleeding, questioning and examination one month after they entered the study, but they did come in after two months on May 17, 1969. At that time, 63 days after they had received vaccine, the son and his father had rubella HAI titers of 1:128 and 1:256, respectively (Table 2). Of the two transmission

controls, the daughter had remained seronegative, but the mother had developed a rubella HAI antibody titer of 1:256.

The daughter received vaccine on May 17, 1969, and her brother received the placebo. All family members were bled again 35 days later on June 31, 1969, at which time all family members had rubella HAI antibody titers of more than 1:256 (Table 2). Because the daughter did not receive rubella vaccine until 63 days after her father and brother (Table 2), the daughter as well as the mother may be considered as a valid transmission control. None of the four family members developed CF antibodies during the 108-day period March 15, 1969–June 21, 1969. During that period, there was no known exposure

TABLE 2.—*Serological Responses of Family Members Following the Introduction of HPV-77, DK-12 Rubella Vaccine*

<i>Vaccinees</i>	<i>Antibody types</i>	<i>March 15, 1969</i>	<i>May 17, 1969</i>	<i>June 21, 1969</i>
Father	HAI	<8(V)*	256	256
	CF	<8	<8	<8
Son	HAI	<8(V)	128(P)†	512
	CF	<8	<8	<8
<i>Transmission Controls</i>				
Daughter	HAI	<8(P)	<8(V)	256
	CF	<8	<8	<8
Mother	HAI	<8	256	256
	CF	<8	<8	<8

* Date vaccine given

† Date placebo given

of any family member to "wild" rubella. Furthermore, none of the four members of the family had any symptoms consistent with clinical rubella.

Discussion

The detection of pharyngeal shedding of HPV-77 or HPV-77 derived live rubella vaccine virus by vaccinees has been reported by other investigators.²⁻⁴ Further, there appears to be a direct relationship between the frequency of pharyngeal shedding of rubella viruses by vaccinees, subsequent to inoculation, and the serologic efficacy of attenuated rubella virus strains.² Although the regular shedding of rubella viruses by vaccinees has caused the potential recognition of spread of vaccine virus, there have been only two reports that spread may have occurred¹¹ and one of those reports was the brief mention of the first subject discussed here.¹ The very low frequency of detection of vaccine virus spread is probably related to transient or intermittent excretion of vaccine virus compared with a more prolonged excretion of "wild" virus in pharyngeal secretions.¹² Nevertheless, sooner or later one would expect to find evidence of vaccine virus spread as the number of vaccinees studied increases. In this report, evidence of rubella vaccine virus transmission to two susceptible contacts under conditions highly conducive to microbial spread, have been presented. In one case, a mentally retarded child, who served as a rubella-susceptible transmission control on a "closed" study ward, acquired the virus from an

immunized contact. The second instance of apparent transmission was to the susceptible mother in an "open" family study. The subject's husband was susceptible to rubella and had received the vaccine, as had her son. Contacts between mentally retarded children and between husband and wife are both likely to be highly favorable for the exchange of pharyngeal microbes.

There is little doubt that the serological responses of the subject serving as a transmission control in our "closed" population study resulted from transmission of HPV-80 rubella vaccine virus from a vaccinee to a control. The vaccinees and the transmission control subjects were isolated on the "closed" study ward for 63 days. None of the other four control subjects developed clinical nor serologic evidence of rubella virus infection. Indeed, three HPV-80 vaccinees failed to show seroconversion. The rubella HAI antibody titers in the infected control subject rose from less than 1:8 to 1:128 between day 30 and day 60—a time sequence which might be said to be consistent with spread of HPV-80 vaccine virus from a vaccinee. In addition, the appearance of a significant HAI antibody titer in the control subject was not accompanied by the appearance of rubella CF antibodies. This lack of a concomitant CF antibody response strengthens the premise that the seroconversion in the control subject was not caused by undetected, inadvertent introduction of "wild" rubella virus onto the study ward. CF antibody responses can be detected following "takes" of live rubella virus vaccines if the antigen used in the CF test is pre-

pared by alkaline buffer extraction of rubella virus infected BHK-12 cells.¹³ However, the "packed cell" CF antigen used by our laboratory has consistently failed to demonstrate CF antibodies in vaccinees although it does result in the detection of CF antibodies in patients with "wild" rubella virus infection. Therefore, the utilization of the "packed cell" antigen in the rubella CF test is useful as a marker of natural infection even though it is a less sensitive test. Thus, we have been able to demonstrate CF antibodies using this antigen only in children with natural rubella virus infection or upon challenge with low tissue culture passage levels of wild rubella virus.¹

Although there was serologic evidence consistent with rubella vaccine virus transmission to the mother in the "open" family group, in such situations it is impossible to be absolutely certain that the mother did not experience sub-clinical infection with "wild" rubella virus. Sporadic cases of rubella were occurring in her community at the time. On the other hand, there was evidence that the mother was infected with vaccine virus: (1) There was no history of exposure to rubella, (2) Neither the mother nor her susceptible daughter developed any clinical evidence of "wild" rubella virus infection, (3) The mother had a significant rubella HAI titer rise without any detectable rubella CF antibody response, and (4) Her susceptible daughter not only failed to show clinical evidence of "wild" rubella virus infection, but also failed to develop any serologic evidence of rubella virus infection.

Despite the two instances of probable vaccine

virus transmission reported here and the single transmission reported by Lefkowitz et al,¹¹ the failure of many published studies to elicit any evidence at all of spread of vaccine virus from vaccinees to susceptible contacts means that such spread is very uncommon. However, the very fact that transmission is rare indicates a real need for concentrated and well-planned surveillance programs in families of vaccinees which should continue until the potential for spread of the vaccine virus is defined and until any possible embryopathic potential of the vaccine virus is ruled out.

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HEARING LOSS FROM INDUSTRIAL NOISE

In people with possible hearing loss from industrial noise, how long must the ear be away from noise before any temporary threshold shift will recover?

Two weeks is mandatory. Some small additional gain may occur in the first month, but very little thereafter—although occasionally in the single-incident trauma, as from an explosion, a slight additional improvement might be recorded for as long as two months. To be on the safe side, one could say that after two months any remaining loss would be considered permanent.

—MACK E. PATTERSON, M.D., Los Angeles
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Specialty Conference

Nephrotic Syndrome

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AND HENRY GRAUSZ, M.D., *San Francisco*

*Based on Medical Grand Rounds at the University of California,
San Francisco*

DR. EARLEY:^{*} This presentation will touch on several aspects of the nephrotic syndrome, including the varied etiologic factors, clinical manifestations, pathophysiologic and histopathologic features, and methods of treatment. In discussing histopathology and therapy, Drs. Hopper and Grausz will rely heavily on the experience with more than two hundred patients with so-called "idiopathic" nephrotic syndrome diagnosed and followed at this institution during the past 14 years.

Definition and Etiology

The nephrotic syndrome results from disorders of the kidney in which large amounts of plasma protein, mainly albumin, are excreted into the urine. If this loss of albumin is great enough to exceed rates of albumin production by the liver then the concentration of albumin in plasma falls and the entire complex of symptoms recognized as the nephrotic syndrome may ensue. It should be emphasized that heavy proteinuria leading to the nephrotic syndrome may be present as the only clinical manifestation of renal disease, or the syndrome may be associated with varying degrees of other manifestations of the underlying

renal disorder, such as azotemia, acidosis and anemia. Also, the nephrotic syndrome may be caused by certain systemic diseases, notably diabetes mellitus, systemic lupus erythematosus and amyloidosis, and in such cases the syndrome can appear together with any of the nonrenal manifestations of the underlying disease.

Although the nephrotic syndrome has been defined exclusively on the basis of a high rate of protein excretion, usually 3.5 grams or more daily, some patients may excrete even larger amounts of albumin without having the symptom complex, while others may have the syndrome while excreting lesser amounts of protein. Nevertheless, the excretion of 3.5 grams or more of albumin daily should be regarded as indicative of the presence of a renal lesion known to result in the nephrotic syndrome, even though the clinical syndrome may not be present.

Table 1 is an abbreviated list of underlying causes of the nephrotic syndrome. It is generally accepted that proteinuria (albuminuria) is indicative of a primary glomerular disease, and any of the glomerulonephritides, at some time in the course of the disease, may be associated with the nephrotic syndrome. However, the syndrome is not a usual feature of acute post-streptococcal glomerulonephritis, rapidly progressing glomerulonephritis or focal glomerulonephritis such as that associated with bacterial endocarditis. A

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TABLE 1.—Summary of Causes of the Nephrotic Syndrome

I. Primary Renal Disease
Glomerulonephritis (post-streptococcal, rapidly progressing)
“Idiopathic” Nephrotic Syndrome (lipoid nephrosis, membranous glomerulonephritis, membranoproliferative glomerulonephritis)
II. Secondary to Systemic Disease
Diabetic Glomerulosclerosis
Lupus Nephritis
Allergic Arteritis (periarteritis, Henoch-Schonlein purpura)
Amyloidosis (primary, secondary, myeloma)
Infections (malaria, syphilis)
Neoplasia (cancer and lymphoma)
III. Specific Toxins or Inciting Agents
Heavy Metals (mercury, bismuth, gold)
Drugs (tridione, paradione, penicillamine)
Allergens (poison oak and ivy, bee sting, snake venoms)
IV. Mechanical
Cardiovascular Disease (constrictive pericarditis, severe right heart failure)
Renal Vein Thrombosis
V. Congenital or Familial
Familial or Congenital Nephrotic Syndrome of Infancy and Childhood
VI. Related to Pregnancy
Pre-Eclampsia
“Recurrent Nephrotic Syndrome of Pregnancy”

relatively large fraction of all patients presenting with the nephrotic syndrome have no underlying recognized cause for the disorder, and these patients have in the past been classified as having an idiopathic nephrotic syndrome. On the basis of glomerular histology and the fixation of fluorescent anti-globulin antibodies, this group can be subdivided into at least three subgroups: lipoid nephrosis, membranous glomerulonephritis, and membranoproliferative glomerulonephritis. In addition to distinct histopathologic differences there also are differences in the clinical course and response to therapy among these subgroups.

Among the systemic diseases causing the nephrotic syndrome, diabetic glomerulosclerosis is probably the most common in this country. However, in some parts of the world where quartan malaria (*plasmodium malariae*) is endemic this may be a common cause of the nephrotic syndrome,¹ and in other areas where tuberculosis or leprosy are prevalent, secondary amyloidosis may be a more common cause. The syndrome frequently occurs in the course of systemic lupus erythematosus (SLE) and with somewhat lesser frequency in the course of the various arteri-

tides.² Renal amyloidosis, whatever the cause, commonly results in the nephrotic syndrome. It should be pointed out that heavy proteinuria in the course of multiple myeloma does not indicate necessarily the presence of renal amyloidosis and the nephrotic syndrome since in this disease the excretion of Bence-Jones protein may reach several grams daily in the absence of heavy albuminuria.

Increased renal venous pressure, as may occur in severe right heart failure or constrictive pericarditis, results in albuminuria which in some instances may be so extensive that the nephrotic syndrome appears and adds to the other manifestations of the underlying cardiovascular disease.³⁻⁵ In such circumstances the syndrome may disappear as venous pressure decreases with improvement in cardiac function. Also, renal venous thrombosis has been associated with the nephrotic syndrome,⁶⁻¹¹ and unilateral thrombosis with ipsilateral proteinuria has been reported.⁹⁻¹¹ However, in most reported patients with the nephrotic syndrome and renal vein thrombosis renal biopsy has demonstrated membranous glomerulonephritis,^{10,11} even in the kidney without venous thrombosis.^{10,11} In such cases it is difficult to attribute the nephrotic syndrome to the venous thrombosis *per se*, and it may be that the underlying renal disorder results independently in the nephrotic syndrome and renal venous thrombosis.¹¹

Allergens such as poison oak, poison ivy, bee sting and snake venom may cause a nephrotic syndrome, and the syndrome is recognized as a complication of certain drugs including the anti-convulsants tridione and paradione^{12,13} and the chelating agent penicillamine.^{14,15} The heavy metals, bismuth, gold and mercury, including organomercurial diuretics, can produce a nephrotic syndrome.^{16,20}

The syndrome may appear in infants due to congenital or familial factors, but these patients usually die and therefore such causes are not a consideration in adults.^{21,22} Albuminuria in the course of pre-eclampsia occasionally may be extensive enough to result in hypoalbuminemia and the nephrotic syndrome.²³ The diagnosis of pre-eclampsia as a cause of the nephrotic syndrome should be based on renal biopsy, since there are reports of patients who have had a nephrotic syndrome only while pregnant and in the absence of other manifestations of pre-eclampsia or

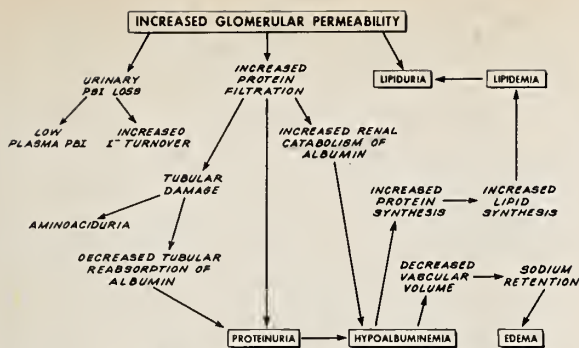


Chart 1.—Pathophysiologic pathways leading to the major manifestations of the nephrotic syndrome.

underlying renal disease.²⁴ It is difficult to judge whether pregnancy in these patients was in some way directly responsible for the nephrotic syndrome or some pre-existing subclinical renal lesions were unmasked during pregnancy.

The nephrotic syndrome has been reported in association with a variety of malignant lesions,^{25,26} but a cause and effect relationship remains obscure. The syndrome has occurred in transplanted kidneys even though the renal disease leading to transplantation was not associated with the nephrotic syndrome.²⁷ It should be pointed out, however, that a nephrotic syndrome is not associated with the characteristic picture of rejection of transplanted kidneys.

Although the list of causes for the nephrotic syndrome is extensive, it is notable that some common diseases of the kidney characteristically are not associated with the syndrome. Among these are pyelonephritis, analgesic nephropathy, nephrosclerosis, familial polycystic disease, "acute tubular necrosis," renal arterial stenosis, obstructive nephropathy and the renal failure of scleroderma.

Pathophysiology (Chart 1)

Proteinuria in the nephrotic syndrome appears to be related to abnormally increased permeability of the glomerular membrane. In adult humans approximately 150 liters of glomerular filtrate are formed daily. This volume of plasma would contain up to 10 kg of protein, but normally not more than 100 to 200 mg of protein appears in the urine each day. Most of this normal urinary protein is derived from renal tubular cells and not from plasma. The normal glomerular membrane functions as a selective filter permitting the filtration at plasma concentration

of non-protein bound molecules with molecular weights less than 6×10^3 . Molecules with molecular weights greater than 40 to 50×10^3 are restricted almost completely from filtration, and substances with molecular weights between these values are filtered at a concentration less than that in plasma. It is widely accepted that in the nephrotic syndrome glomerular permeability is increased enough to permit filtration into the tubular lumen of plasma albumin and to a lesser extent the larger plasma globulins. Although increased glomerular permeability alone could adequately account for proteinuria, the possibilities of decreased tubular reabsorption of filtered protein and even leaking of protein across the tubule from peritubular plasma cannot be excluded as factors contributing to proteinuria.

Fluid sampled by micropuncture from Bowman's space in normal rats and dogs has been found to contain plasma proteins at concentrations as high as 20 mg per 100 ml and 6 mg per 100 ml, respectively.^{28,29} These same studies indicated that this "filtered" protein is reabsorbed along the course of the proximal tubule. In a more recent study of rat proximal tubular fluid utilizing different techniques for measuring protein, the concentration in filtrate was found to be 1 mg or less per 100 ml.^{29a} Although these concentrations of protein in glomerular filtrate are only a fraction of a percent of the concentrations in plasma, if this filtered protein was not reabsorbed but excreted into the urine it could amount to the loss of as much as 1.5 to 30 grams per day in man, if human glomerular filtrate contains protein within a similar range of concentrations. The likelihood that the human kidney also filters and reabsorbs protein, at least in disease states, has been suggested by indirect techniques. If in a subject with mild albuminuria the concentration of albumin in plasma is progressively increased by infusion, the rate of excretion of albumin may increase in linear relationship with the increase in plasma concentration, similar to the relationship between the concentration of glucose in plasma and the rate of excretion of glucose.^{31,32} If these excretion rates are extrapolated back to zero plasma concentration, one obtains an apparent reabsorptive rate in the case of glucose of approximately 300 mg per minute (the familiar transport maximum for glucose) and for albumin an apparent reabsorptive rate of about 30 mg per minute, suggesting that this capacity for

albumin reabsorption exists. For several reasons it seems possible that small amounts of plasma protein are filtered and reabsorbed normally, and if so it is possible that altered tubular reabsorption of albumin could contribute to proteinuria in the nephrotic syndrome, although it is unlikely that such a mechanism accounts predominantly for the proteinuria.

When concentrated albumin is infused into patients with the nephrotic syndrome and hypoalbuminemia the rate of protein excretion may increase proportionately more than the increase in concentration of protein in plasma.³¹ In other words, the clearance of protein may increase when albumin is infused (Chart 2). This phenomenon could be due to an increased glomerular permeability to albumin or possibly to saturation of a tubular reabsorptive mechanism as filtered albumin increases due to the increased concentration in plasma. However, infusion of dextran produces a similar increase in clearance of protein at a time when the concentration of albumin in plasma is decreased due to dilution by the infused dextran solution. In this latter case the concentration of albumin in glomerular filtrate could not be increased as a simple consequence of increased concentration in plasma, and therefore the increased clearance of albumin is due most likely to increased entry of albumin into the tubular lumen, possibly as a consequence of stretching the glomerular capillary³¹ membrane as the vascular volume is expanded. Observations of this type provide additional indirect evidence that proteinuria in the nephrotic syndrome is due largely to a leakage of protein across the glomerular membrane. Also, the experiment shown in Chart 2 emphasizes the futility of treating patients with the nephrotic syndrome with infusion of albumin. In the patient illustrated, infusing albumin to increase the concentration in plasma to 3 grams per 100 ml would have resulted in the excretion of more than 80 grams of albumin daily if this plasma concentration could be maintained.

It has been suggested that the degree of selectivity of protein excretion in the nephrotic syndrome may relate to prognosis and the response to therapy.³² Highly selective proteinuria is defined as the virtual absence in urine of globulins above a molecular weight of 150×10^3 , with albumin accounting for more than 90 percent of the urinary protein. Poorly selective proteinuria is present when 10 percent or more of the urinary

EFFECT OF PLASMA VOLUME EXPANSION ON PROTEINURIA IN NEPHROTIC SYNDROME

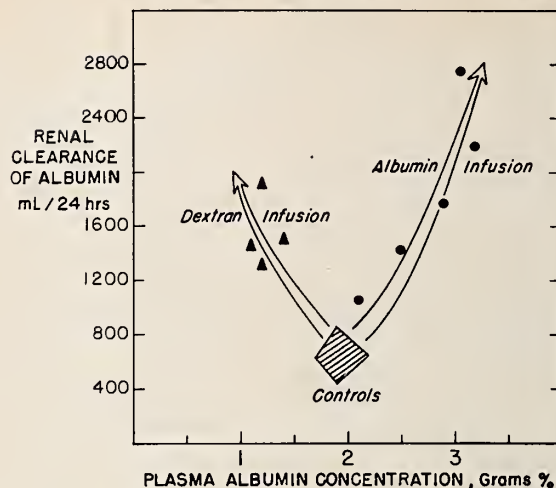


Chart 2.—Effects of Infusion of Albumin or Dextran in a Patient with the Nephrotic Syndrome due to Lipoid Nephrosis. Rates of albumin clearance before infusion are indicated by the shaded area. In one study 25 grams per 100 ml of human albumin was infused to increase plasma albumin concentration from about 2 grams to as high as 3 grams per 100 ml. This resulted in more than a four-fold increase in albumin clearance. Due to the increase in plasma albumin concentration this represented an eight-fold increase in the rate of albumin excretion. In a separate study plasma volume was expanded by infusing iso-oncotic dextran which resulted in a similar increase in albumin clearance despite the fall in plasma albumin concentration due to dilution by the dextran solution. These changes indicate that expansion of the intravascular volume increases albumin clearance, presumably by increasing the rate of filtration of albumin.

proteins are globulins, some of which may have molecular weight greater than 400×10^3 . When selectivity and glomerular histology have been studied in the same patient with the nephrotic syndrome it appears generally that patients with lipoid nephrosis show highly selective proteinuria whereas patients with membranous or proliferative glomerulonephritis show poorly selective proteinuria.³³ Therefore, the extent of selectivity of proteinuria may relate to the underlying disease and not to the severity of any single disease. There is no convincing evidence that the degree of selectivity of proteinuria in patients with "idiopathic" nephrotic syndrome affords diagnostic or prognostic information as meaningful as that obtained from a histologic diagnosis.

Hypoalbuminemia

Hypoalbuminemia in the nephrotic syndrome is the consequence of the loss of albumin (uri-

nary loss plus catabolism) in excess of the rate of production of albumin by the liver. As the concentration of albumin in plasma falls the absolute rate of excretion decreases until a new steady state is reached between the rate of production and the rate of excretion plus catabolism, at which time the concentration in plasma stabilizes at a new low value. Of interest is the fact that hypoalbuminemia is maintained in some patients in whom the excretion of albumin may be only a few grams daily, less than the expected rate of hepatic production of albumin. It has been demonstrated in patients with the nephrotic syndrome that the fraction of the total albumin pool catabolized daily exceeds that in normal persons, even when the rate of loss into urine is taken into consideration.^{34,35} It has been suggested that albumin may leak across other capillary beds such as in the gut where it would be catabolized and the amino acids would be reabsorbed. However, there is no proof that this is so. Several lines of evidence indicate that the kidney is a site of protein catabolism,³⁶⁻³⁹ and in animals with an experimentally produced nephrotic syndrome it has been demonstrated that the kidneys may be an important site of increased destruction of albumin.^{37,39} In normal circumstances the kidneys may contribute negligibly to albumin catabolism, but in the presence of increased filtration of albumin a significant fraction of reabsorbed albumin may be destroyed by the renal tubules, thus contributing to the development of hypoalbuminemia.

Edema

Edema is the most prominent outward manifestation of the nephrotic syndrome and often is the first evidence of disease noted by patients with idiopathic nephrotic syndrome. Under normal conditions sodium excretion is regulated so as to equal the dietary intake of sodium and maintain the volume of extracellular fluid, including the intravascular volume, within narrow limits.⁴⁰ It appears that changes in the excretion of sodium require changes in the relationship between filtered and reabsorbed sodium and that such changes are initiated by changes in the extracellular fluid volume *per se*.⁴⁰ Increases in extracellular fluid volume resulting from infusion or ingestion of sodium lead to depressed tubular reabsorption and increased excretion of sodium. Decreases in extracellular fluid volume as would

result from sodium deprivation or hemorrhage lead to increased tubular reabsorption and decreased excretion of sodium. The pathways linking changes in the volume of extracellular fluid and changes in sodium reabsorption and excretion are complex and appear to involve a combination of humoral and hemodynamic factors.⁴⁰ The event leading to renal retention of sodium in the nephrotic syndrome must be the decreased intravascular volume resulting from the decreased plasma protein osmotic pressure. The sodium and water retained will only partially restore the intravascular volume and most of the retained fluid is distributed in the interstitial spaces as edema. Edema fluid can be mobilized, the vascular volume increased and the excretion of sodium increased by infusing concentrated albumin to increase plasma protein osmotic pressure.⁴¹ However, for reasons discussed earlier this is not a satisfactory method for treating patients with the nephrotic syndrome.

The question is asked frequently why persons with familial analbuminemia do not have edema as do patients with hypoalbuminemia due to the nephrotic syndrome. Since the distribution of volume between the vascular and interstitial compartments depends on the gradients of both hydrostatic pressure and protein osmotic pressure across the capillary wall, one is forced to conclude that the low protein osmotic pressure is balanced by a reduction in capillary hydrostatic pressure in patients with familial analbuminemia.⁴² For unknown reasons such a compensation does not occur or is incomplete in patients with the nephrotic syndrome.

Once sodium retention has occurred and edema is present in a patient with the nephrotic syndrome the intravascular volume may be restored to a nearly normal value,⁴³ and the excretion of sodium may balance with the dietary intake. Only during the period of sodium retention and edema formation would it be expected that the intravascular volume would be small. However, it should be emphasized that even when such a steady state has been achieved the patient with the nephrotic syndrome may have a diminution of his intravascular volume as a consequence of diuretic-induced sodium excretion and failure to replenish the intravascular volume by mobilizing edema fluid. Such a diminution of intravascular volume, whether occurring spontaneously as a consequence of severe hypoalbuminemia or as a

result of forced diuresis, may be reflected by a decrease in renal function (filtration rate and blood flow) which is not due directly to progression of the underlying renal disease.⁴⁴

Lipiduria

Lipiduria occurs in the nephrotic syndrome irrespective of the underlying cause. Lipid may appear in the urine as droplets of neutral fat or as cholesterol esters, either free in the urine or contained within casts of degenerative tubular epithelial cells. Cholesterol esters account for the familiar "maltese crosses" seen as doubly refractile bodies when viewed under polarized light. Lipid laden degenerative tubular epithelial cells, known as oval fat bodies, also are readily identified under polarized light. Lipiduria appears to correlate more closely with heavy proteinuria than it does with the presence or absence of hyperlipemia, and it is not clear how the lipid enters the tubular fluid. In the presence of increased glomerular permeability cholesterol and other lipids may be filtered into the urine even in the absence of hyperlipemia. Tubular epithelial cells may accumulate lipid either as a result of reabsorption from tubular fluid or from the peritubular plasma and then release their contents into the tubular fluid or be sloughed intact into the urine. Lipiduria may be present in renal disease with moderate to severe proteinuria before other manifestations of the nephrotic syndrome appear.

Thyroid function

Thyroid function has been thought to be abnormal in patients with nephrotic syndrome. This suggestion was based initially on the presence of hypometabolism (low basal metabolic rate) and hypercholesterolemia. However, it was observed nearly fifty years ago that these patients tolerate large doses of thyroid hormone without developing hypermetabolism, a response not expected in patients with true hypothyroidism.⁴⁵ The hypercholesterolemia appears to be a feature of the generalized hyperlipidemia resulting more directly from the abnormal albumin metabolism in the nephrotic syndrome and therefore need not be attributed to hypothyroidism. Moreover, it is possible that the low rate of oxygen consumption may be due to decreased heat loss consequent to the insulating blanket of edema and shunting of blood away from the skin because of

decreased blood volume. Nevertheless, it has been demonstrated repeatedly that the concentration of protein bound iodine (PBI) may be abnormally low in patients with the nephrotic syndrome,^{46,47} and this has led to attempts to unravel the mechanism of abnormal thyroid function in these patients. The urine contains relatively large amounts of PBI and the half-life of injected thyroxine may be shortened, due largely to losses in the urine.⁴⁷ The thyroidal uptake of inorganic iodine is normal or increased^{46,47} and the output of thyroid hormone may be increased by administering thyrotrophic hormone (TSH).⁴⁷ From these observations it would be logical to propose that excessive loss of thyroid hormone into the urine results in low circulating levels of hormone which lead to hypometabolism and increased TSH secretion. However, since the thyroid gland is capable of further response to administered TSH it seems necessary to postulate some failure of the pituitary-thyroid axis in patients with the nephrotic syndrome, and it has been suggested that this abnormality may relate in some way to the state of protein depletion.⁴⁷ The picture is complicated further by the possibility that the relative contributions of urinary loss of hormone and an inadequate TSH-thyroid response to tissue hypometabolism may differ from patient to patient and in the same patient at different stages of the disease. Finally, it is possible that the amount of circulating hormone available to peripheral tissue could be normal in some patients despite a low plasma PBI as a result of hypoproteinemia and decreased binding of thyroid hormone in plasma.

Aminoaciduria

Aminoaciduria occurs occasionally in patients with the nephrotic syndrome and has been attributed to defective proximal tubular reabsorption of filtered amino acids.^{48,49} Presumably, continued filtration and reabsorption of plasma proteins lead to damage of the proximal tubular epithelium since some of the reported patients did not have an underlying renal disease known to produce aminoaciduria. In a few patients a picture of more complete proximal tubular dysfunction resembling the de Toni-Fanconi syndrome has been observed (aminoaciduria, hyperphosphaturia, glucosuria, hyperchloremic acidosis).^{48,49} This pattern of proximal tubular dysfunction has been observed also in patients with

gammopathies associated with increased excretion of globulin fragments and has been attributed also to an effect of the filtered (and reabsorbed) protein to damage the proximal tubule.⁵⁰ There is no information available to indicate the frequency of such proximal tubular dysfunction in patients with idiopathic nephrotic syndrome characterized by the nearly exclusive excretion of albumin, but it would seem to be uncommon. When proximal tubular dysfunction appears together with the nephrotic syndrome in a patient with multiple myeloma or some other gammopathy, the nephrotic syndrome may be due to associated renal amyloidosis, while proximal tubular dysfunction could be due to the independent effects of filtered globulin fragments. For this reason one should search for urinary Bence-Jones protein and underlying myeloma in the patient presenting with the combination of a nephrotic syndrome and the de Toni-Fanconi syndrome.

At this point I would like to turn to Dr. Richard J. Havel, who will discuss in detail some aspects of the disorders of lipid metabolism associated with the nephrotic syndrome.

Lipid Metabolism

DR. HAVEL: * Dr. Earley has pointed out that hypoalbuminemia in the nephrotic syndrome results from loss of albumin through the glomerulus. Other plasma proteins are also lost in amounts that are roughly in inverse proportion to their molecular dimensions. Among the various lipoproteins, only the smallest class, the high density lipoproteins (HDL) with molecular weight about 300×10^3 , is lost to an appreciable extent. This loss may contribute to the lipiduria. Glomerular leakage of the other classes of lipoproteins is negligible. These classes include the cholesterol-rich low density lipoproteins (LDL) with molecular weight about 26×10^3 and the triglyceride-rich very low density lipoproteins (VLDL) and chylomicrons which are even larger. The lack of appreciable filtration of these lipoproteins explains the failure of lipoprotein levels to fall in the nephrotic syndrome but it does not explain the variable and sometimes massive accumulation of abnormal amounts of certain lipoprotein classes in blood plasma. I will discuss evidence that the proteinuria leads to increased protein synthesis in the liver and indicate how

this can at least partly explain the hyperlipoproteinemia. Before I do so, I should indicate that not all hyperlipidemia** in renal disease represents the nephrotic syndrome. For example, moderate hypercholesterolemia and hypertriglyceridemia occur early after the onset of acute glomerulonephritis.⁵¹ This may represent a non-specific response to fat-mobilization induced by the stress of the illness or the associated catabolic state, similar to that observed frequently after acute myocardial infarction. Mild hyperlipidemia is also a common accompaniment of acute and chronic renal failure.^{52,53} Usually, triglyceride levels are increased but cholesterol levels remain normal and, as expected, the concentration of triglyceride-rich VLDL is elevated. In acute renal failure, stress-induced fat-mobilization may underlie the hyperlipidemia. Chronic renal failure is accompanied by a state of hyperinsulinism with insulin resistance, a situation commonly accompanied by increased concentration of VLDL in blood plasma (examples: obesity, lipodystrophies, use of contraceptive steroids) so that it may represent an example of hyperlipidemia related to diminished response of tissues to the action of insulin.⁵⁴ Nowadays, many patients with nephrotic syndrome are given substantial quantities of glucocorticoids. These compounds also induce a state of insulin resistance and hyperinsulinism and can themselves induce a hyperlipoproteinemia similar to that observed in untreated patients with nephrotic syndrome.⁵⁴ Therefore, the relationship between hyperlipoproteinemia and nephrotic syndrome per se can be evaluated only in untreated subjects.

Such a study was carried out a number of years ago at the National Heart Institute.⁵⁵ It was found that the hypercholesterolemia and hypertriglyceridemia were accompanied by increased concentrations of LDL, VLDL or frequently, by combined elevation of both classes. A predominant hypercholesterolemia was associated with increased concentrations of LDL and a clear serum while predominant hypertriglyceridemia was associated with increased concentrations of VLDL and lactescent serum. Levels of cholesterol and LDL were inversely related to those of serum albumin. As the level of albumin fell, concentration of cholesterol rose gradually and then,

**This term is equivalent to hyperlipoproteinemia since virtually all plasma lipids are carried as macromolecular aggregates containing various lipids in combination with specific proteins.

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with extreme hypoalbuminemia (below 1 gram per 100 ml) it rose rapidly. A similar relationship was noted for triglyceride, except that its concentration rose very little until hypoalbuminemia became severe; then it, too, rose very rapidly.

The lipoprotein patterns, as expected, showed predominant elevation of LDL with mild to moderate hypoalbuminemia and predominant elevation of VLDL with very low levels of albumin. Concurrent work by Gitlin and his associates at Harvard Medical School with ^{131}I -labelled lipoproteins from normal and nephrotic subjects indicated that a substantial fraction of VLDL is converted to LDL.⁵⁶ Subsequent work has confirmed and extended this observation^{54,57} and it now appears that the LDL arise to a large extent as catabolic products of VLDL. This occurs when VLDL, which are the vehicles for transporting triglycerides from the liver, unload these triglycerides in extrahepatic tissues.

Recent studies have shown that VLDL, albumin and very likely many other plasma proteins synthesized in the liver share a common pathway of synthesis and secretion. For VLDL, the pathway can be visualized directly with the electron microscope,^{58,60} since the lipid-rich precursors of VLDL are large and readily take up the usual electron-dense osmium tetroxide stain. These precursors first appear near the junction of the rough and smooth endoplasmic reticulum. The rough (ribosome-containing) reticulum is the site at which plasma proteins are synthesized and it appears that they move within its cisternae to the smooth endoplasmic reticulum where lipids are mainly synthesized. Specific lipophilic proteins combine with and stabilize the lipid to form particles of about 300-1000 Å diameter. These particles then move from the smooth endoplasmic reticulum into connecting tubules of the Golgi apparatus where certain carbohydrate moieties are added to the proteins of the nascent lipoproteins. The particles then appear to accumulate in dilated saccules of the Golgi apparatus which separate to form secretory vesicles. The vesicles, in turn, migrate to and fuse with the plasma membrane of the cell, and, in the process, liberate their contents into the space of Disse which lies beneath the sinusoidal endothelium (upper left, Figure 1). Finally, the particles pass through fenestrations in this porous lining to enter the blood stream.

With the aid of cell fractionation techniques, Peters and associates⁶¹ have recently shown that essentially the same pathway outlined for VLDL is followed by newly synthesized albumin—namely, passage from the rough to the smooth endoplasmic reticulum and thence to the Golgi apparatus before reaching the blood. This entire process of synthesis and secretion takes place in a matter of a few minutes. By a technique of gradient ultracentrifugation of a subcellular preparation of rat liver, a fraction rich in secretory vesicles can be obtained. Following rupture of the membranes of this fraction, the contents can be harvested. This material contains not only the nascent VLDL which closely resemble their counterparts in the blood⁶² but also a large number of other plasma proteins which are detected with anti-rat serum.⁶³ Thus, it appears that albumin, VLDL and other plasma proteins that are synthesized in the liver may be secreted into the blood by a common mechanism. It is reasonable, therefore, to consider the possibility that certain mechanisms regulating the synthesis of these proteins may be controlled in common. Experiments using a model of human nephrotic syndrome—that produced by injecting rats with an antiserum to rat kidney—have provided support for this possibility. In such rats, increased synthesis of albumin and of VLDL has been shown using liver slices and perfused livers.⁶⁴ In the case of VLDL, this increased synthesis has been shown to apply to both the lipid and protein parts of the macromolecular complex. In another model of nephrotic syndrome in the rat—that induced by injection of the aminonucleoside of puromycin—electron micrographs of the liver have shown substantially increased numbers of VLDL precursors within the profiles of the smooth endoplasmic reticulum and Golgi apparatus,⁶⁵ providing morphological support for the biochemical evidence just cited (Figure 1). Additional biochemical studies indicate that in the experimentally produced nephrotic syndrome, there is increased mobilization of amino acids from muscle to liver accompanied by decreased conversion of amino acid-carbon to carbohydrate and increased conversion to protein and to certain lipids^{64,66} The process appears to constitute a “protein diabetes” in which the liver attempts to compensate for the substances lost in the urine by increasing their biosynthesis.⁶⁴

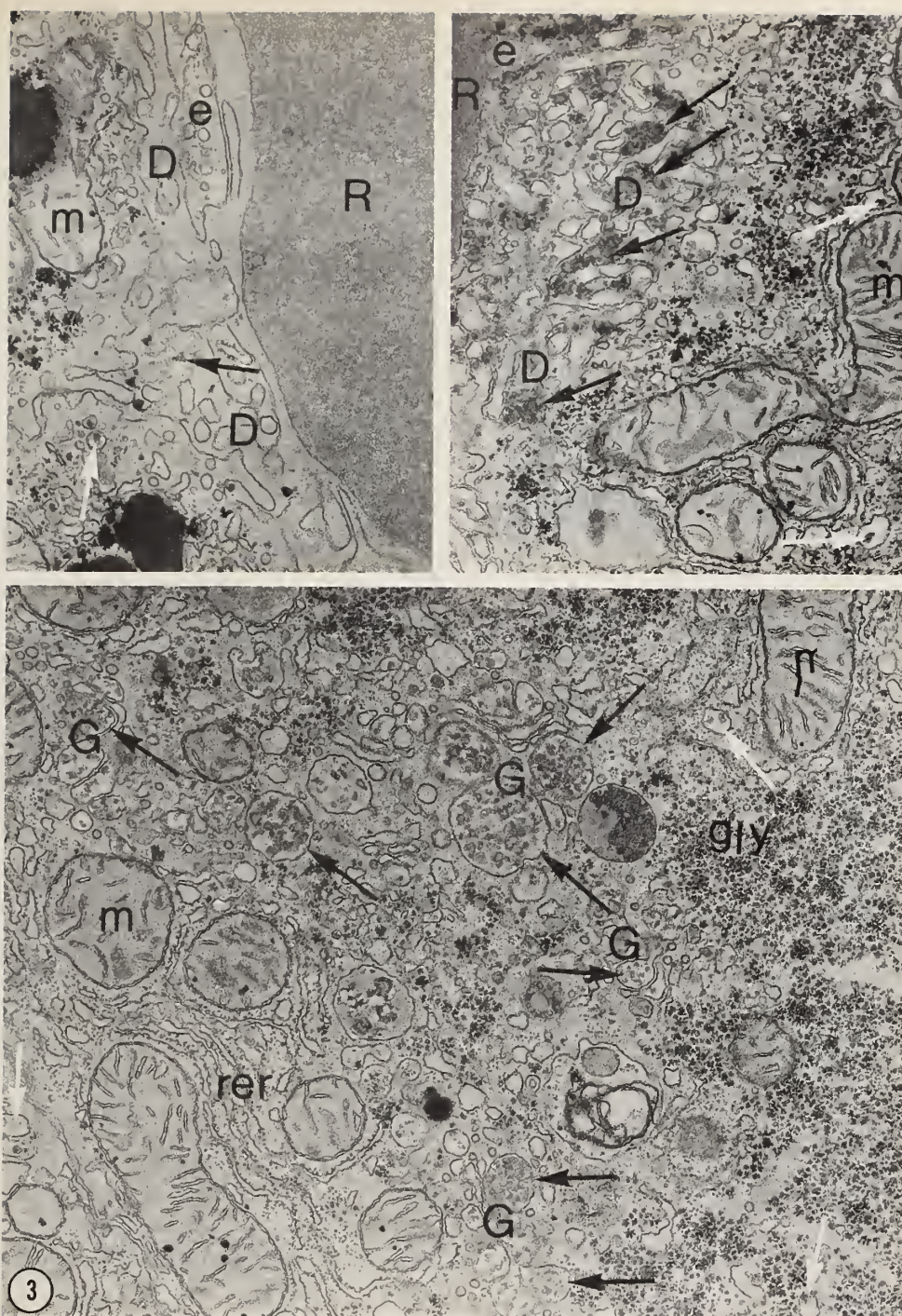


Figure 1.—Electron micrographs of rat liver (26,000 X). D=space of Disse; e=endothelial cell; G=Golgi apparatus; gly=glycogen; m=mitochondria; rer=rough-surfaced endoplasmic reticulum; R=red blood cell.

Upper left—Space of Disse of control rat showing several VLDL particles (black arrow). A few particles can be observed within the intracellular membranes of the liver cells (white arrow).

Upper right—Aminonucleoside nephrotic animal. The spectacular accumulation of lipoprotein particles (black arrows) in the experimental animals appears to occlude the space of Disse (black arrows). Particles are observed within the endoplasmic reticulum of the liver cell (white arrows).

Lower center—Portion of a liver cell from a nephrotic animal. Lipoproteins are observed in extraordinary numbers within the saccules and secretory vesicles of the Golgi complexes (black arrows) as well as in the smooth surfaced endoplasmic reticulum (white arrows).

The signal responsible for setting this compensatory mechanism into motion has not been determined. It has been suggested that reduced oncotic pressure of the plasma may be such a signal. Infusions of albumin into patients with nephrotic syndrome cause transient falls in the concentration of VLDL and infusions of dextran have similar effects.⁶⁷ There is also evidence that infusion of dextran into rabbits reduces hepatic synthesis of albumin,⁶⁸ consistent with operation of a feed-back system related to oncotic pressure. How such a mechanism might operate is unknown.

There is no compelling evidence that the mechanisms leading to hyperlipoproteinemia in experimentally produced nephrotic syndrome in the rat apply to the nephrotic syndrome in man. The similarities of lipoprotein pattern in the human and murine disorders together with the clear relationship between the magnitudes of the albuminuria and hyperlipoproteinemia strongly suggest that compensatory increase in hepatic biosynthesis of plasma proteins occurs in both. The tendency for both VLDL and LDL to be elevated in patients with the nephrotic syndrome accords with an increased rate of lipoprotein biosynthesis, but the relationship between the varying patterns of hyperlipoproteinemia and severity of the protein leak described earlier is poorly understood. By analogy with certain other hyperlipoproteinemic states, it is possible to consider that with increasing rates of secretion of VLDL, the capacity for utilizing triglycerides in extrahepatic tissues tends to become saturated, thus limiting conversion of VLDL to LDL. This possibility is consistent with the reciprocal relationship between the concentration of VLDL and LDL that is generally observed. A specific derangement of the VLDL-LDL conversion is also possible. When albumin concentrations are very low, free fatty acids such as those which are produced during catabolism of plasma triglycerides or during mobilization of fat from adipose tissue tend to be carried to an increased extent by lipoproteins.⁶⁹ Conceivably, these free fatty acids could interfere with the triglycerides from VLDL or with some other part of the conversion process.

Treatment of the hyperlipoproteinemia of nephrotic syndrome is not usually considered apart from that of the primary disorder. In most cases, this is appropriate since the hyper-

lipoproteinemia subsides rapidly when the glomerular leak is repaired. However, when the syndrome is long-standing and when the hyperlipoproteinemia is aggravated by administration of glucocorticoids, there may be an increased risk of symptomatic atherosclerotic disease, as in other situations accompanied by high levels of plasma lipids. Little work has been done to evaluate methods for lowering lipoprotein levels in human nephrotic syndrome but recent work in rats with aminonucleoside-induced nephrotic syndrome indicates that p-chlorophenoxyisobutyrate may be effective.^{70,71}

DR. EARLEY: For more than a decade now, there has existed at this institution an excellent opportunity to study the clinical and histopathologic relationships in patients with nephrotic syndrome. This has resulted from Dr. James Hopper's long interest in the disorder, his application of percutaneous renal biopsy years before the procedure became as widely accepted as we know it today, and his close working relationship with our electron microscopists—first Dr. Marilyn Farquhar and more recently Dr. John Lee. Dr. Hopper will address himself to the histologic diagnosis of the nephrotic syndrome.

DR. HOPPER: * The most reliable differentiation of nephrotic syndromes can be made by means of renal biopsy and study of the tissue by light, fluorescence, and electron microscopy. Unfortunately, neither the abnormal physiology relating to nephrotic states nor the chemical changes which occur in blood or urine, suffice to differentiate among the varied etiologies of the syndrome. Differentiation is highly important as a guide to both treatment and prognosis. For example, most clinicians agree that in a patient who has nephrotic syndrome due to diabetic glomerulosclerosis, treatment should consist of appropriate management of the diabetes, including dietary adjustments and restrictions, and possibly diuretics for the edema. There is considerable evidence indicating that treatment with glucocorticoids may result in overall clinical deterioration in the patient with diabetic glomerulosclerosis. On the other hand, relatively large doses of steroids are generally advocated as treatment for the nephrotic syndrome accompanying systemic lupus.^{72,73} Nephrotic syndromes accompanying amyloidosis

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may also be worsened by glucocorticoid therapy⁷⁴ while attempts to eliminate the cause of amyloidosis (such as treating underlying infections) may be beneficial.⁷⁵ It has been suggested that anticoagulants may be useful in preventing intrarenal venous thrombosis sometimes seen in renal amyloidosis^{76,77} and anticoagulation is the treatment of choice^{10,11} in established renal vein thrombosis.

As suggested by Kark⁵ and others,^{2,78} nephrotic states may be divided into two broad categories: (1) due to primary renal disease and (2) secondary to systemic disease involving the kidneys. The important systemic etiologic factors, as mentioned by Dr. Earley, are diabetes mellitus, systemic lupus erythematosus (SLE) and primary and secondary amyloidosis, with frequency of occurrence in this sequence at our medical center. These lesions usually can be easily differentiated by renal biopsy and light microscopy. However, the added value of electron microscopy in differentiating the renal lesion of SLE deserves special comment. In this disease we⁷⁹ and others have found a very high incidence of "virus-like particles" in the endothelial cytoplasm of both glomerular and tubular capillaries (Figure 2). In a retrospective study the incidence of these particles was 97 percent, while in a prospective study we are finding them in all renal lesions accompanying lupus. Thus, although they are not entirely specific, we think these particles are very helpful in diagnosing lupus nephritis.

In the presence of a clearly established systemic disease such as diabetes mellitus or SLE renal biopsy usually confirms that the nephrotic syndrome is due to the underlying disease. However, in the absence of a demonstrated systemic or primary renal disease known to cause the syndrome renal biopsy is particularly important, both from the point of view of therapy and prognosis. The incidence of these idiopathic lesions varies considerably among different series, from one geographic area to another and also between childhood and adult populations. In childhood and infancy lipid nephrosis accounts for 50 to 75 percent of all idiopathic nephrotic syndromes; proliferative glomerular nephritis makes up most of the remainder, and membranous glomerulonephritis is rare. Moreover, assigning one of these three diagnoses in a given patient requires that renal

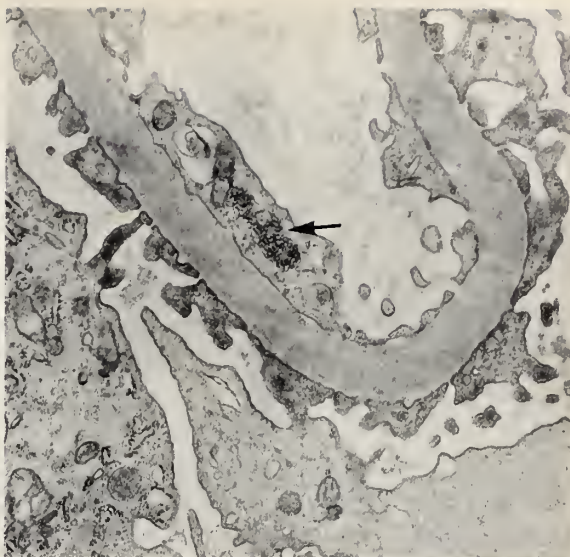


Figure 2.—Electron microscopic view of a portion of a glomerular capillary from a 42-year old woman with systemic lupus erythematosus who had normal renal function and mild proteinuria. By light microscopy her renal lesion was interpreted as a mild focal glomerulonephritis (glomerulitis). The arrow is in a capillary lumen and points to a honeycomb "virus-like" particle enclosed in a faintly outlined membrane located within endothelial cell cytoplasm. Magnification 9500X.

biopsy be performed, and even then the diagnosis can be influenced by whether or not the tissue is studied by a combination of light and electron microscopy and immunofluorescence.

Our own series⁴³ of idiopathic nephrotic syndrome in adults (age 14 to 82 years) has now reached 200 cases over a 14-year period. All have had renal biopsy and the tissue was studied by both light and electron microscopy.* The distribution of specific glomerular lesions within this group is shown in Table 2. Table 2 also shows the incidence of these lesions in a group of adult patients with idiopathic nephrotic syndrome studied in England by Sharpstone et al.⁸⁰ Black et al⁸¹ in a multi-center study, also in England, report an incidence of lesions similar to that noted by Sharpstone. Although there is a difference in the frequency of membranous and proliferative glomerulonephritis in England

*Dr. J. C. Lee and Dr. W. Rosenau performed the electron microscopy and fluorescence microscopy, respectively. Two cores of tissue are taken routinely from different areas of the same kidney through a single skin puncture. The specimens are immediately divided and placed in distilled glutaraldehyde for electron microscopy and into 10 percent Zenker-formol solution for light microscopy, and iced for immunofluorescence study. For light microscopy sections are cut 2 to 4 microns thick which permits meaningful evaluation of glomerular cellularity. Thin sections of Araldite embedded tissue are cut for light microscopy and ultra-thin sections for electron microscopy, permitting study of the same glomerulus by both techniques.

TABLE 2.—Incidence of Specific Histologic Lesions in Adults with Idiopathic Nephrotic Syndrome at the University of California San Francisco and in the Series of Sharpston et al⁸⁰ in London

Lesion	UCSF		London	
	No. of Cases	Percent	No. of Cases	Percent
Lipoid	50	25	15	30
Membranous*	60	30	6	12
Proliferative	70	35	29	58
Unclassified	20	10	—	—
TOTAL:	200	100	50	100

*Includes membranoproliferative lesions in the UCSF series.

and California, the incidence of lipoid nephrosis is similar in both areas. In contrast, Schreiner²⁴ did not include the diagnosis of lipoid nephrosis in a series of 111 patients, all of whom were studied histologically. We believe the latter difference is related to the criteria used in establishing the histologic diagnosis, including fluorescence and electron microscopy. Our use of the term lipoid nephrosis is to describe the glomerular lesion that has been called variously "nil disease," implying little or no abnormality by light microscopy (upper left, Figure 3); "Earle's epithelial cell disease" (vascularization of epithelial cells and fusion of their foot processes along the capillary basement membrane as seen by electron microscopy); "foot process disease"; "minimal lesion"; "true nephrosis"; and "childhood nephrosis" (since this appears to be the most common lesion in childhood nephrotic syndrome). In addition the glomerular capillary basement membrane appears normal in terms of thickness and electron density (upper right, Figure 4). Also, in our own series there has been an absence of fixation of fluorescent tagged anti-human-globulin (IgG, IgM, and IgA) and complement (B_{1c-a}) to glomerular structures.*

Lest it be assumed that lipoid nephrosis always remains a "nil" lesion, it should be emphasized that severe glomerular sclerosis can occur, sometimes rapidly (even within a year), whereupon the lesion becomes obvious even by light microscopy.⁸³ This advanced lesion is characterized by glomerular capillary basement membrane thickening, and in particular by deposition of basement membrane-like material

together with fibrin in the mesangial areas, until the entire glomerulus is sclerosed and non-functional. Even in the presence of these advanced histologic changes anti IgG, IgM, and IgA and complement fixation cannot be demonstrated.

Membranous glomerulonephritis also is characterized by coalescence of glomerular epithelial-cell-foot-process, as are all nephrotic states. In addition, there is deposition of soluble antigen-antibody complexes adjacent to the epithelial-cell or urinary-space side of the glomerular capillary basement membranes (therefore sometimes called epimembranous disease (Hamburger). These deposits are demonstrable both by electron microscopy (upper right, Figure 4) and immunofluorescence techniques (lower right, Figure 4). By light microscopy alone a membranous lesion can be mistaken for lipoid nephrosis (lower left, Figure 3).

Proliferative glomerulonephritis is characterized by variable proliferation of any of several cellular elements within the glomeruli; endothelial, mesangial, or epithelial; sometimes with invasion of white blood cells (exudation and sometimes with proliferation of the epithelial cells of Bowman's capsule to form crescents. All glomeruli may be involved or there may be focal and segmental involvement. As in membranous glomerulonephritis, proliferative lesions are generally thought to be due to soluble antigen-antibody immune complexes. These can be demonstrated by electron microscopy and often by fluorescence microscopy. Proliferative lesions have been divided into a number of sub-groups,^{84,86} any of which may be accompanied by nephrotic syndrome. There is considerable controversy concerning the response of the various proliferative lesions to glucocorticoids, cytotoxic agents or anticoagulants. Responses to treatment are variable, none have been entirely effective and there is a need for further study with well matched controls. Proliferative lesions usually can be adequately identified by light microscopy. A well defined proliferative lesion with crescent formation is shown in the upper right panel of Figure 3.

DR. EARLEY: To conclude this session Dr. Henry Gausz will discuss methods of treatment of the nephrotic syndrome, with emphasis on idiopathic nephrotic syndrome and the importance of histologic diagnosis in the selection of specific therapy.

*Recently, however, Gerber and Paronetto⁸² have observed deposition of IgE in a comma pattern in glomeruli of patients with lipoid nephrosis without fixation of complement. They similarly observed deposition of IgE in a membranous lesion, although in a different pattern from that observed in lipoid nephrosis. Localization of IgE has not been confirmed by electron microscopy.

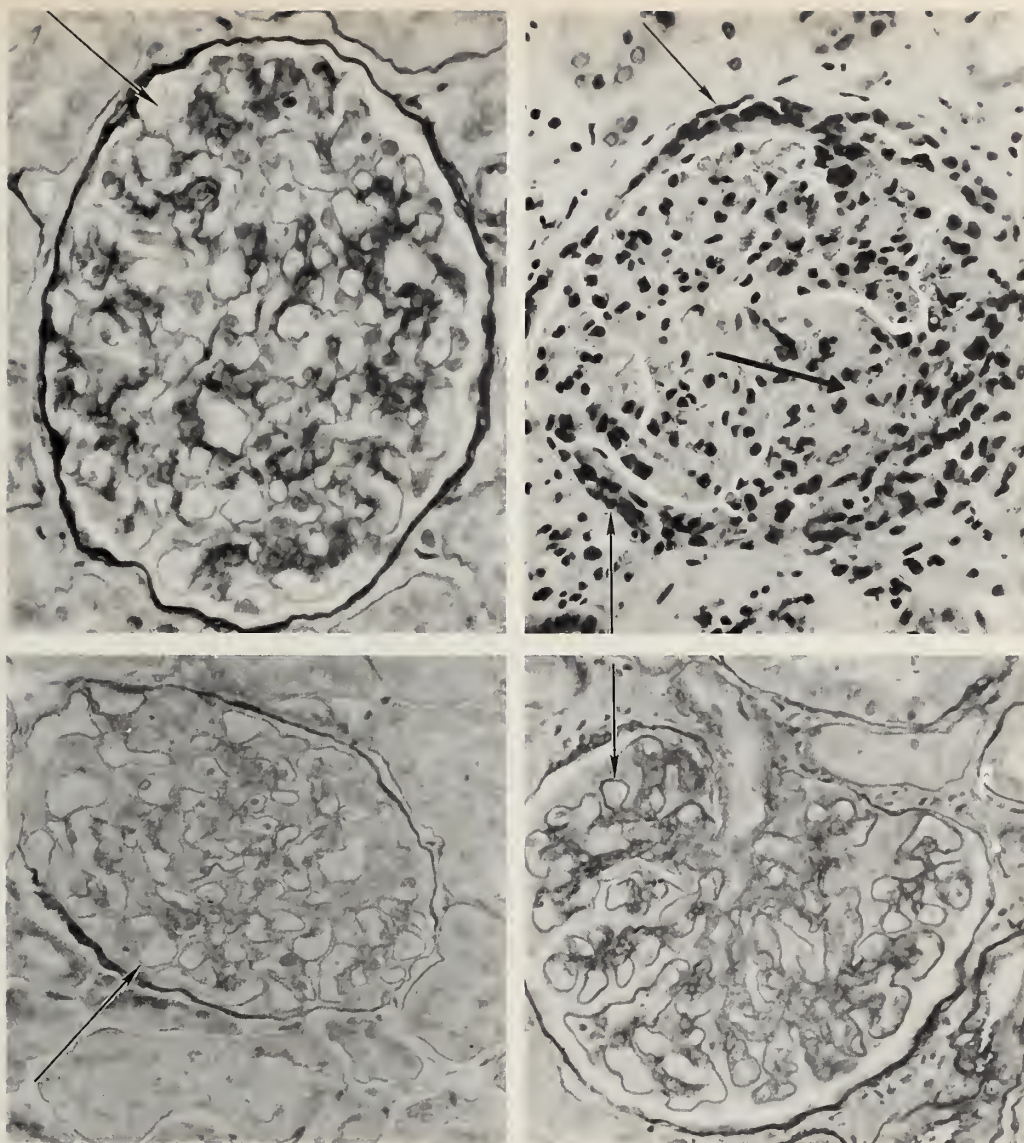


Figure 3.—Upper left—Typical glomerulus from a 34-year-old woman with nephrotic syndrome due to lipoid nephrosis. Biopsy was obtained one month after apparent onset. By light microscopy and periodic acid Schiff (PAS) stain this glomerulus could be considered normal. Capillaries are widely open, and capillary basement membranes are of normal and uniform thickness (arrow). Endothelial, mesangial and epithelial cells are not increased in number. As is typical for lipoid nephrosis, no immunofluorescence could be demonstrated. Magnification 500X.

Upper right—Typical glomerulus from a 44-year-old man with nephrotic syndrome and an advanced proliferative glomerulonephritis. A large proliferating crescent is seen (large arrow) and early crescent formation is seen in other areas along Bowman's capsule (fine arrows). There are areas of cellular proliferation in the glomerular tuft. As compared to upper left figure capillary lumens are poorly defined. H & E stain, magnification 500X.

Lower left—Early membranous glomerulonephritis in a 40-year-old man approximately five months after onset of nephrotic syndrome. The arrow points to a capillary basement membrane. Comparison of the basement membranes in this figure and in that of the upper left figure shows that they are of similar thickness. Like the glomerulus in the upper left figure this glomerulus also could pass as normal by light microscopy. However, fluorescence microscopy demonstrated anti-IgG globulin and complement in a granular pattern along the capillary basement membranes and electron microscopy revealed a typical although early membranous lesion. PAS stain, magnification 500X.

Lower right—Typical glomerulus from a 30-year-old man showing advanced membranous nephropathy by light microscopy. Capillary basement membranes (arrow) are decidedly thickened, giving the loops a rigid appearance. As in the lower left figure, fluorescence and electron microscopy revealed changes typical of membranous nephropathy. This biopsy was the fourth of a series and was performed approximately five years after onset of the renal nephrotic syndrome. PAS stain, magnification 500X.

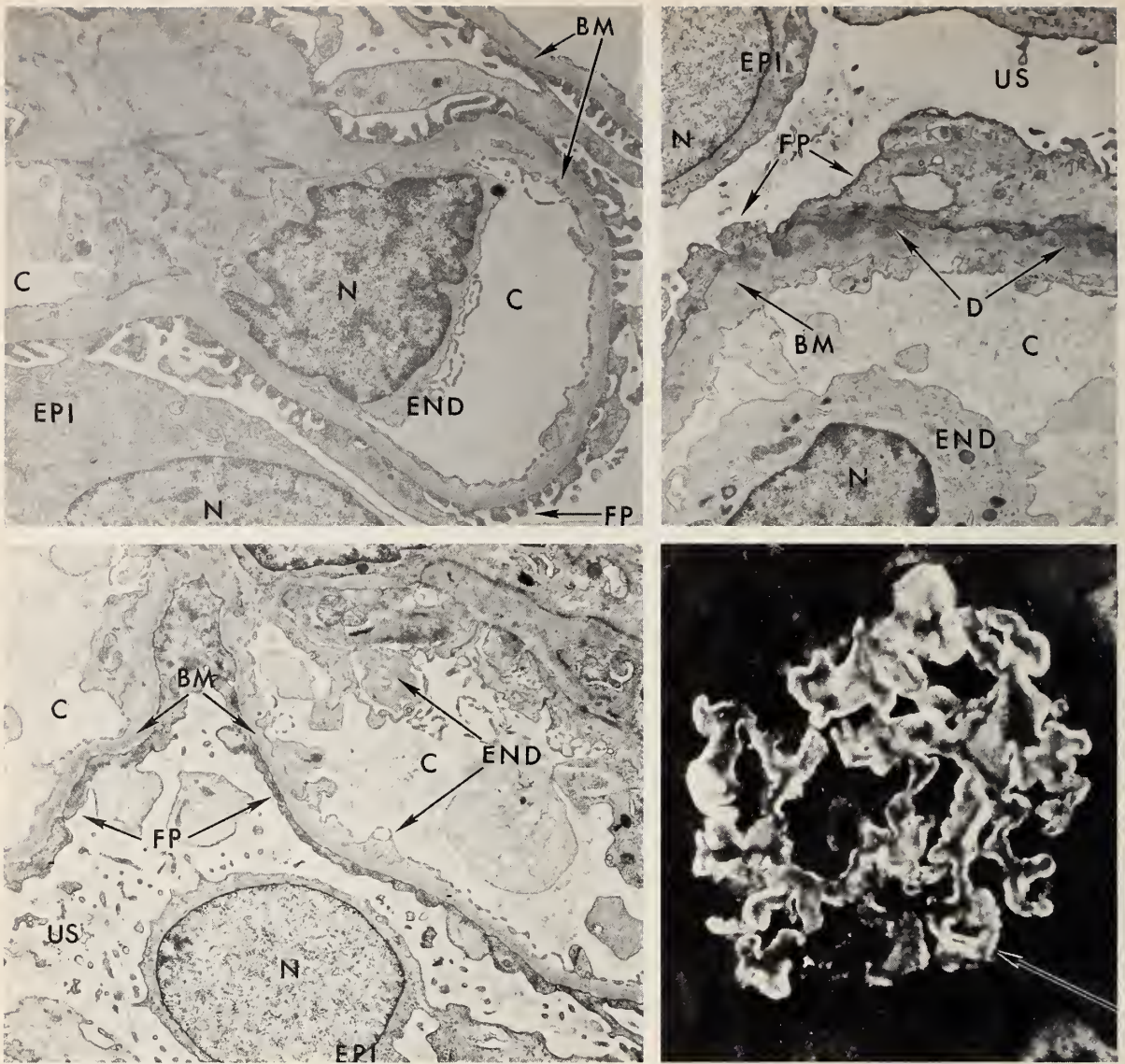


Figure 4.—Upper left—Electron microscopy of renal biopsy specimen from a healthy 19-year-old man. Open capillary loops (C) are seen as well as an endothelial (END) and epithelial (EPI) cell with their respective cytoplasm and nuclei (N). Foot processes (FP) which derive from epithelial cell cytoplasm can be seen in apposition to the capillary basement membrane (BM). The continuity of these foot processes with the epithelial cells is lost in most area because the plane of the section is at a different level. Urinary (Bowman's) space (US). Magnification 9600X.

Upper right—Electron microscopy of glomerulus from a 22-year-old man with membranous nephropathy. Legend the same as upper left figure. Note that basement membranes are thick and irregular and in addition to coalescence of epithelial cell foot processes, there are multiple dense deposits (D) between the basement membrane and the foot processes. These dense deposits are identified as the substance responsible for immunofluorescence and is thought to be soluble antigen-antibody complexes. Magnification 8312X.

Lower left—Electron microscopy of a glomerulus from a 37-year-old man with lipoid nephrosis of approximately a year's duration. Legend is the same as above. Note that glomerular basement membranes are not thickened but foot processes are coalesced against the epithelial surface of the capillary basement membranes. Magnification 9200X.

Lower right—Immunofluorescent study of the same specimen shown at upper right (membranous glomerulonephritis). The presence of anti-IgG and complement (β_2 -microglobulin) is demonstrated and can be seen outlining glomerular capillary basement membranes in a granular pattern typical of this lesion (arrow). Magnification 500X.

Treatment of Nephrotic Syndrome

DR. GRAUSZ:^{*} When the nephrotic syndrome occurs as a manifestation of an underlying systemic disease such as diabetes mellitus, multiple myeloma or lupus erythematosus, the major therapeutic measures should be directed toward controlling or reversing the primary disease. In the case of diabetic glomerulosclerosis or renal amyloidosis there is little or no evidence that the nephrotic syndrome is reversible. When the nephrotic syndrome is due to lupus nephritis, it may improve or disappear if therapy is successful in arresting or reversing activity of the systemic disease.^{72,73} However, even in the absence of treatment that can correct the pathologic processes leading to the nephrotic syndrome, other supportive therapeutic measures are important.

In the absence of important azotemia, a high dietary intake of protein should be instituted in order to minimize the negative nitrogen balance resulting from heavy proteinuria. This often neglected measure can retard muscle wasting and other consequences of protein depletion. When the nephrotic syndrome coexists with azotemic renal failure the intake of protein may have to be restricted to prevent or delay symptoms of uremia such as nausea, vomiting and acidosis. As azotemia progresses, proteinuria may decrease and the nephrotic syndrome disappear, presumably as a consequence of declining glomerular filtration rate which reduces the amount of plasma protein filtered.

Sodium retention and the formation of edema are hallmarks of the nephrotic syndrome and in most patients it is appropriate to restrict the dietary intake of sodium. Moreover, the current availability of powerful diuretic agents affords an approach to the management of edema which makes the role of dietary sodium restriction less important. There are reasons to believe that patients with the nephrotic syndrome may be more responsive to some of the diuretic drugs than are patients with sodium retention due to other causes.⁸⁷ It should be emphasized that maintaining the patient free of edema by combinations of sodium restriction and diuretics probably does nothing to correct the basic physiologic disturbance of the nephrotic syndrome even though the patient may be physically and psychologically more comfortable after losing edema fluid. Furthermore, the use of powerful diuretics carries

the risk of intravascular volume depletion with consequent electrolyte abnormalities (hyponatremia) and worsening of overall renal function. These serious complications are more of a danger to the patient than is the cosmetic disadvantage of some edema, if the latter is necessary to maintain an adequate circulating blood volume.

Treatment of the nephrotic syndrome with ACTH or glucocorticoids was introduced in the early 1950's, prompted by earlier evidence that adrenal function influences proteinuria in the rat.⁸⁸⁻⁹⁰ During the past twenty years numerous reports have appeared in the literature on the efficacy of steroid therapy for idiopathic nephrotic syndrome.^{43,81,91-94} Until recently it has been nearly impossible to assess the results of such specific therapy. Even now, some newer modalities of treatment, although apparently efficacious, remain unproved. Nevertheless, it has become clear at this point, largely as a result of increasing use of percutaneous renal biopsy, that improvement in some facets of the disease can be expected from some of these therapeutic measures in some patients with idiopathic nephrotic syndrome.

The remainder of this discussion will be devoted to the treatment of patients with idiopathic nephrotic syndrome, which includes all patients with the nephrotic syndrome due to a primary renal disease which is not attributable to a recognized inciting event or agent, such as post-infections glomerulonephritis, nephrotoxins, and others (Table 1). Patients with idiopathic nephrotic syndrome can be divided into three or four groups on the basis of histopathologic features of the glomerular lesion. As discussed by Dr. Hopper, our experience has been analyzed on the basis of three classifications: (1) lipid nephrosis, (2) membranous glomerulonephritis with or without proliferative changes and (3) proliferative glomerulonephritis without characteristic membranous changes. Earlier literature on the prognosis and response to therapy of patients with idiopathic nephrotic syndrome is difficult to analyze since in many instances these different glomerular lesions have been treated as a single group.^{92,93} Our experience and the more recent experience of others leaves little doubt that prognosis and response to therapy differs among the sub-groups of idiopathic nephrotic syndrome. This fact alone emphasizes the importance of renal biopsy.

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I would like to discuss the results of therapy in a group of 200 patients with idiopathic nephrotic syndrome followed at this institution, primarily by Dr. James Hopper, Jr., during the period 1957 through 1971. No patients with systemic disease or recognizable causes of the nephrotic syndrome are included. On the basis of light and electron microscopy, as described earlier, 50 patients (25 percent) were diagnosed as having lipoid nephrosis, 60 (30 percent) had membranous glomerulonephritis and 70 (35 percent) proliferative glomerulonephritis (Table 2). The patients ranged in age from 14 to 82 years. Supportive therapeutic measures were not rigorously standardized but did include the following: (1) A dietary intake of protein of 80 to 130 grams daily, unless contraindicated by the onset of azotemia, (2) a dietary intake of sodium between 200 and 1000 mg daily, and (3) intermittent diuretic therapy (thiazides, furosemide and the like) together with supplemental potassium when indicated.

Steroid therapy was instituted according to one of two schedules:

1. *Continuous therapy*: Prednisone (or an equivalent dose of another glucocorticoid) was given daily in a single dose of 50 to 90 mg. If there was no decrease in the rate of excretion of protein at the end of one week, the daily dose was increased by 20 mg each successive week until protein excretion decreased or a daily dose of 160 mg of prednisone was reached. If no decrease in the rate of protein excretion occurred at the end of one week at this highest dose of prednisone, the daily dose was decreased by 20 mg decrements each succeeding week until medication was terminated. After four to six weeks off treatment, therapy with prednisone was re-instituted at a daily dose of 80 to 100 mg and continued for another four to six weeks. However, if at any time during the initial or second phase of treatment with prednisone, urinary protein excretion decreased to 1 gram per 24 hours or less, therapy was changed to 100 or 120 mg of prednisone on alternate days and continued for four to twelve months.

2. *Interrupted therapy*, which was used initially in some patients. This consisted of 100 to 200 mg of prednisone on alternate days for two to six months, after which the dosage was decreased 10 to 20 percent monthly.

Response to therapy

We classified the responses to therapy in our patients according to the criteria suggested by Maxwell et al⁹⁵ as follows:

Class A: Disappearance of proteinuria, loss of edema and return to normal of all biochemical parameters.

Class B: Decrease in proteinuria to less than 3.5 grams per 24 hours, maintenance of serum albumin at 2.5 grams per 100 ml or higher, and a decrease in serum cholesterol to values less than 400 mg per 100 ml.

Class C: Complete or partial loss of edema or some decrease in proteinuria, but no improvement in other biochemical abnormalities.

Class D: No improvement in any biochemical or physical abnormalities.

In addition, we have chosen the designation *cure* for all Class A responses which persisted for at least one year off treatment.

We have reviewed the course of 31 of the patients with lipoid nephrosis. In two patients, no therapy was given because the patient was lost to follow-up early in the course of study. In two other cases no treatment was given because the patients improved spontaneously during the initial period in hospital. (At present these two patients have been free of proteinuria for five and eight years, respectively. One has since had two uncomplicated pregnancies.) The remaining 27 patients were treated with glucocorticoids alone or, in some instances, with cytotoxic agents in combination with a lower dose of the steroid. This latter form of combined therapy was used when there was less than a Class A response to one of the regimens of prednisone alone as described above. Twenty-one of the 27 patients had a class A response at least once during the course of their illness. Of the remaining six patients, five had Class B responses and only one showed no response to therapy.

This long term study has led us to favor continuous treatment with prednisone followed by an interrupted course (a single dose each 48 hours). If the patient cannot be kept in hospital for continuous high dose treatment, we then choose the 48-hour schedule initially, and this also has proved effective.

Since some patients may not tolerate such high doses of steroids, an attempt was made to assess the value of immunosuppressive therapy as the

initial treatment in five patients with lipid nephrosis. These patients were given a single dose (0.3 to 0.4 mg per kilogram of body weight) of nitrogen mustard. Two of the five had a Class A response within six weeks following the treatment and three showed no response to this therapy. Although this form of treatment is difficult to evaluate from so small a group of patients, we feel that immunosuppressive therapy alone should be used as initial treatment in lipid nephrosis only if steroids are strongly contraindicated.

Treatment of membranous glomerulonephritis is far less satisfactory and also is more difficult to evaluate. In a study by Randall et al,⁹⁶ 14 patients with proved membranous glomerulonephritis were followed for a year without any evidence of spontaneous improvement. In other studies of idiopathic nephrotic syndrome as a single group, spontaneous remissions may have occurred in about 18 percent of the patients.⁹² It is likely that in such a group about 30 percent of the patients have lipid nephrosis, a disease which may have a spontaneous remission rate as high as 50 percent. Therefore, the spontaneous remission rate of membranous glomerulonephritis must be less than the 18 percent observed for idiopathic nephrotic syndrome as a single group. In fact, the spontaneous remission rate for membranous glomerulonephritis alone may be nil. However, it is our experience that an occasional patient with membranous glomerulonephritis does undergo a remission of the clinical disease when treated with steroids or immunosuppressive agents or both. Without knowing whether or not remissions do occur in patients with membranous disease, such "responses to therapy" are impossible to evaluate. Nevertheless, at our present stage of understanding, it seems justifiable to treat patients who have membranous glomerulonephritis with some combination of high dose steroids and immunosuppressive agents such as azathioprine (Imuran®). In my opinion, however, such therapy should not be continued indefinitely in the absence of clear-cut improvement, since the complications of therapy may result overall in earlier mortality than would occur from the disease without treatment. Randall reported recently that in a group of 20 patients with membranous glomerulonephritis treatment with cyclophosphamide (1 to 2 mg per kg of body weight per day) for six to twelve months

resulted in lessening of proteinuria. Follow-up renal biopsy in two of the patients showed improvement and dissolution of the intramembranous electron-dense deposits characteristic of the lesion.⁹⁶ Such histologic evidence of improvement is very important since therapy with steroids may be associated with decreased proteinuria in patients with membranous glomerulonephritis, even though the histologic lesion may remain unchanged or even progress. Although Randall's results are encouraging, it is too soon to state with certainty that cyclophosphamide is the treatment of choice in membranous glomerulonephritis. Nevertheless, his preliminary report should stimulate additional studies of the use of this agent in membranous glomerulonephritis.

Although many means of treatment have been tried for proliferative glomerulonephritis, there is little or no evidence that any form of therapy clearly arrests or reverses the course of this disease. Steroids, immunosuppressive agents and heparin have been used, either singly or in combination, and on occasions one or the other of these agents has appeared to be efficacious. However, the use of these forms of therapy in proliferative glomerulonephritis must still be considered experimental and at the present time there is no specific treatment which predictably will alter the usual relentless downhill course of proliferative glomerulonephritis.

DR. EARLEY: We have attempted in this presentation to touch on the protean clinical and pathophysiological consequences of a single and seemingly simple defect—increased permeability of the glomerular membrane to protein. The nephrotic syndrome, possibly as much as any other disease, exemplifies the extensive interrelationships and somewhat delicate balance that may exist among several metabolic and organ systems. Some of these are often not appreciated clinically as the continuum of a single pathologic process. Past and current studies of various aspects of this syndrome have on occasion resulted in information which has added to our understanding of such diverse extrarenal processes as protein and lipid synthesis and the control of intravascular volume. Undoubtedly there is still much to learn from this simple lesion that is brimming over with pathophysiology.

Dr. Hopper and Dr. Grausz have emphasized the importance of renal biopsy and a histologic diagnosis in those patients who have a nephrotic

syndrome in the absence of one of the recognized systemic or renal causes. Among such patients renal biopsy is of more than academic interest since prognosis and response to therapy relate closely to the underlying renal changes. By histologically identifying these different underlying lesions we are only now forming a basis for intelligently studying pathogenesis, natural history and responses to specific therapy of the several ill-defined renal diseases known collectively as idiopathic nephrotic syndrome.

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TREATMENT FOR WHIPLASH HEADACHE

The post-trauma or post-whiplash headache, in contrast to what a lot of insurance adjusters say, actually does exist. It's a muscle tension or muscle contraction type of headache. It's true that these headaches may be more protracted and prolonged in people with a basic underlying personality defect, but they also occur in the most stoic of individuals so there must be some organic factor involved.

Then there's the turnpike headache, in the joker who drives 700 miles in 10 hours and walks into his hotel room with his head down between his shoulders and his trapezius muscle like a piece of whalebone. He'll have a headache all night long with that. He may also have associated symptoms of stiff neck, lightheadedness, cricopharyngospasm, and sweaty palms—all the other symptoms of the tense nervous individual.

In treating these (and other) tension-type headaches, the ergotamine preparations have no place and no effect. But the analgesics such as Fiorinal® seem to work very well. Heat and massage to the tense muscles may help in some cases; and in the more severe and incapacitating cases, traction and a neck brace may become necessary.

—ROBERT J. CAMP, M.D., Miami
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MEDICAL STAFF CONFERENCE

Medical Complications of Heroin Addiction

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* We are pleased to have Dr. Charles Becker with us today to discuss the very important problem of heroin addiction.

DR. BECKER:† Ten months ago a 20-bed Detoxification Unit was opened at San Francisco General Hospital to aid patients who had acute and chronic alcohol problems and needed care in a hospital. Since that time approximately 700 patients have been admitted and some 200 consultations have been answered concerning many different drug abuse and clinical pharmacology problems. In attempting to be responsive to the community problem of alcoholism we learned that the public and private agencies which referred alcoholic patients to our unit also had a need to refer narcotics abusers. The scope of the Detoxification Unit was therefore broadened to admit patients needing management of complications of heroin abuse. This expansion has led to a broad learning experience, both challenging and frustrating, for the students, house staff and paramedical personnel. Today I would like to review for you our experience with these patients and to emphasize the magnitude of heroin abuse, the chemical and pharmacological features of heroin and the medical sequelae of heroin addiction.

*Lloyd H. Smith, Jr., M.D., Professor and Chairman, Department of Medicine.

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Vocabulary of the Addict

One of our first observations was that we would have to broaden our vocabulary to communicate with these patients. When asking for *Charlie* a patient in withdrawal period was not referring to a person but requesting cocaine. *Cotton* is the filter that is used in the spoon of the heated heroin while it is being drawn up into the needle. Some times this cotton is soaked and used as a marginal source of narcotic. The *spike* is the needle used to inject heroin. *Flash* or *rush* refers to the acute effects of the intravenous use of heroin which occur a few seconds after injection and are one of the prime goals of the narcotic user. *Monita* is a Spanish-Mexican slang word for the milk-sugar adulteration of heroin. *Bonita*, used in its special sense mainly in Harlem, is another term for the milk-sugar quinine adulterants. (The quinine is used to prevent the buyer from tasting top grade heroin, which has a bitter taste.) Intravenous quinine is associated with dilation of the blood vessels of the face and contributes to the flash. When we first heard *P.G.* we thought it meant Procter & Gamble, but we soon learned that it was argot for paregoric, which contains 0.421 percent of opium. When the paregoric is heated the camphor alcohol is evaporated, leaving the opiate. The intravenous use of paregoric is associated with sclerosing of

veins. It has been pointed out that people with injection sears in the neck most often are users of paregoric, the anteeubital veins having been sclerosed by the use of P.G. *Hype* is the entire paraphernalia that is needed to inject heroin. *Speedball* refers to a combination injection of an *upper* (cocaine) and a *downer* (heroin). *Blues* are amobarbital (amytal®) or pyribenzamine, *yellow*s are pentobarbital (Nembutal®) also called *yellow jackets*, and *reds* are secobarbital (Seconal®) and *whites* are benzedrine. *Rainbows* is a term for an assorted color of barbiturates of all varieties, and *crystals* are methedrine. Some knowledge of this argot is necessary to communicate with the heroin addict.

Incidence of Heroin Addiction

How prevalent is this problem of heroin addiction? One of us here could conclude that it was endemic, while another might think it rare, depending upon our rotations within the University hospital medical residency program. For example, in survey of a 12-month period of admissions to Moffitt Hospital we found a total of four patients who had a diagnosis of heroin abuse, in one of them heroin addiction as the primary diagnosis, and the other three had been transferred from the San Francisco General Hospital to Moffitt Hospital for heart surgery. In a comparable period, with a comparable number of admissions, there were several hundred patients admitted to the San Francisco General Hospital for heroin-related problems. A review of newspaper statistics reveals a range in the reported number of heroin addicts in the United States from 125,000 to 250,000. In San Francisco it is estimated there are between 5,000 and 10,000 heroin abusers. One of the most distressing aspects of the heroin problem is that a minimum of 10 to 15 percent of American servicemen are using high-grade, inexpensive heroin in Vietnam. These servicemen are then returning to the United States and finding the heroin quality is inferior and the cost much greater to maintain a comparable habit.

A recent review by Fort¹ suggests that 1 percent of college students have tried heroin and that in a Berkeley community 5 to 8 percent of the high school seniors had tried heroin.¹ A recent editorial in *Science* pointed out that drug abuse, primarily with narcotics, is the leading cause of death in New York City in the age

group 15 to 35 years. The same editorial pointed out that there were at least 900 deaths a year related to heroin abuse.² In the city of San Francisco there were 56 reported deaths from heroin overdose last year, according to the coroner's office. One explanation for this high death rate may be the wide range of drug strength. The Office of the Medical Examiner in New York City recently analyzed 132 street samples of all drugs purported to contain heroin and found that 12 contained no heroin at all and among the remainder the concentration ranged from less than 1 percent to 77 percent. In California the average concentration of street heroin is approximately 2 percent.

Physicians are at special risk of narcotic abuse. Many articles have emphasized that between 1 out of 40 to 1 out of 100 physicians use hard narcotics in a regular way.³

Senator Hughes of Iowa, who has been a strong proponent of legislation to deal with drug abuse and alcohol problems, recently estimated that there is a 10 billion dollars per year economic loss from the use of narcotics. St. Luke's Hospital in New York recently compared the cost of maintaining 81 addicts on and off methadone therapy and estimated a net saving to society of more than \$800,000 when the addicts were maintained on methadone. In spite of the magnitude of the problem of heroin abuse, there are only ten to twenty thousand patients in any treatment program.

Source of Heroin

What is heroin and where does it come from? The exact date when the mind-altering effects of the use of the extracts of the opium poppy plant were discovered is not known. The discovery is often attributed to the Egyptians, who used tincture of opium to prevent excessive crying in children. Greeks and Romans were aware of the mind altering effects of some of the parts of the poppy plant. Opium was carried to Persia and China in the 9th Century by Arab traders and soon achieved wide popularity. In 1803 a young German pharmacist isolated and described an opium alkaloid that he named morphine, after Morpheus, the Greek god of dreams. Between 1834 and 1858 two so-called "opium wars" were fought and won by the British when Chinese officials attempted to stop trade and seize many of the opium exports. With the invention of the

hypodermic needle in 1840 began the much more severe variety of compulsive narcotic drug use which became rampant during the Civil War in the United States. In an attempt to treat medically the growing narcotic addiction problem, acetylation of the morphine molecule was successfully performed in 1898, leading to the "magic cure" of opium addiction, namely heroin. It should be emphasized that for years heroin was considered a safe, nonaddicting substitute for morphine. Gradually the tremendous mind-altering effects of the intravenous use of heroin became known. International travel by young Americans during World War I, World War II, the Korean and Vietnam wars exposed more and more individuals to these effects of heroin. Currently most opium is obtained from Turkey, Burma and Thailand, shipped to illicit laboratories in Europe where the morphine base is converted to heroin, which is shipped to the United States.

Heroin is a very light, white, bitter chemical which may be adulterated or combined with lactose-mannitol and quinine to mask its bitter taste. Brown heroin is characteristically derived from Mexican sources. In Turkey 20 pounds of raw opium will bring a farmer approximately \$300, and by the time the final product reaches the United States it is worth \$250,000. Heroin is often injected subcutaneously ("skin-popped") or applied to the nasal mucosa ("snorted") before intravenous or "mainline" therapy is attempted.

Since tolerance to heroin develops rapidly, the cost of effective amounts soon becomes unbearable and the patient's life-style centers around obtaining enough money to buy what he needs. To support such a growing habit the heroin addict must classically work in any or several of four occupations—"deal, steal, pimp or whore." It should be emphasized that patients who seek help in the hospital for detoxification or for medical sequelae of the use of narcotics are really addict failures: They are sick because they have failed to obtain the narcotics. Most heroin addicts are "well" and "hustling" to support their habit.

Definition of Addiction

No word has caused more confusion and misunderstanding than *addiction*. To most pharmacologists, addiction has three components, namely a behavior component referring to psychological craving for a drug; a second component involv-

ing a physical dependence on the drug with withdrawal symptoms occurring when the medicine is discontinued; and a third component of tolerance whereby progressively more drug is required to achieve the same effect.

In recent years it has become clear that some drugs, commonly referred to as addicting, are not actually addicting according to the above definition. These drugs are now referred to as entailing "psychological dependence," more commonly known as habituation. Habituation refers to an individual's becoming accustomed to an agent through regular usage so that when the drug is no longer available he becomes restless, irritable or ill at ease. Certainly all of the mind-altering drugs can with regular use lead to psychological dependence, but whether dependence on the drug is significantly impairing the user's life function and whether withdrawal symptoms and tolerance have developed needs further evaluation in each patient. Because of the controversy in definition, most physicians in the field have preferred to refer to heroin addicts as "compulsive narcotic users." Regardless of definition, heroin addiction involves a rapid tolerance to the drug. The explanation for the dramatic increase in dose requirements, which may approach 100-fold, is not well understood but is a pharmacological characteristic of many narcotic drugs.

Chemical Features of Heroin

The narcotic alkaloids occur in the sticky brown gum that is scraped from the surface of an unripe seed pod of the poppy plant. Generally the raw alkaloids are placed in two chemical categories: phenanthrene derivatives which characterize morphine and codeine, and the benzyloquinolone alkaloids representing papaverine-like drugs. Heroin, diacetylmorphine, has substituted acetyl groups in the R_1 and R_2 positions of the phenanthrene nucleus with an unsaturated double bond in positions 7 and 8, and hydrogens in positions 3 and 4. The chemical structure of the opium alkaloids is often written to emphasize the common structure involving a tertiary nitrogen, a short hydrocarbon chain, and a flat aryl group. Pharmacology texts classically describe a hypothetical receptor surface which can accept the narcotic agent but not a mirror image. Narcotic antagonists can also attach to the receptor and reduce the potency of the agonists.⁴

Heroin is rapidly hydrolyzed to monoacetyl-

morphine (MAM), which in turn is hydrolyzed to morphine. In adult patients the blood-brain barrier tends to impede the entry of morphine into the brain. Because it is more lipid-soluble than morphine, this barrier is considerably less effective against heroin, and heroin therefore gives a better "rush-flash" and more rapid action. Most current evidence now suggests that morphine is responsible for the pharmacological actions of heroin. Heroin is primarily excreted in the urine, largely as free and conjugated morphine, and 10 percent is excreted in the bile. Heroin is approximately 2 to 4 times as potent as morphine in relieving pain.⁴

Pharmacological Effects of Heroin

The pharmacological effects of heroin are striking. Within seconds after the intravenous injection of the medication there are dramatic effects—sensations in the upper abdominal region caused by pylorospasm, deepening of the voice, and central nervous system depression associated with nodding, euphoria and drowsiness. With larger doses, there is suppression of respiration, heart rate and blood pressure. It is important to emphasize that the hypotensive effects of narcotics in general are enhanced by the phenothiazines. We have been impressed with the frequency with which heroin addicts are given phenothiazines by unsuspecting physicians and then have pronounced hypotensive effects from intravenous heroin. The patients may become hypothermic and spinal fluid pressure will increase. Histamine is released, leading to urticaria or unusual cutaneous sensations. This may be very disturbing to some addicts and often varies with the purity of the preparation. The cough reflex is suppressed and if vomiting occurs the upper airway may be unprotected and lead to aspiration pneumonia. From a clinical point of view, tolerance may develop to many of the above pharmacological effects of heroin, but fortunately little tolerance develops to the pupillary constriction and the overall gastrointestinal response of constipation. The contraction of the pupils in a comatose patient is a key physical finding in diagnosing acute narcotic overdoses.

Diagnosis and Treatment of Acute Heroin Overdose

Acute heroin overdose is frequently seen in the Mission Emergency Room at the San Francisco

General Hospital when new supplies of more potent heroin become available in the streets. It is also very common that the patient who is admitted to hospital for concomitant medical problems or detoxification has withdrawal symptoms and then returns to his previous habit with a dramatically decreased tolerance. Then if immediately on release he uses the same amount he was using before, he may become acutely comatose with slow, shallow, irregular respirations, a slow pulse, decreased blood pressure and small pupils. The key is to observe the patient for needle marks, including careful observation of the genitalia, the tongue and between toes as important occult portals of entry. We have observed at least ten patients who have been using narcotics in the hospital by injecting the drug into intravenous lines. A patient who becomes comatose and has contraction of pupils while in the hospital may have received illicit narcotics. The treatment of the acute intoxication depends upon expert respiratory support and the judicious use of narcotic antagonists. These antagonists themselves can exert narcotic action if given in excess quantities. The relation of agonist and antagonist is usually described as being competitive, and the relationship is generally viewed as displacement of the agonist from the receptor sight. Nalorphine (Nalline®) is administered in a dose of 2.5 to 5 mg and is usually dispensed in 1 and 2 ml ampules of 5 mg per ml. Levallorphan tartrate (Lorfan®) is administered in a dose of 0.5 to 1.0 mg and comes in 1 ml and 10 ml vials of 1 mg per ml. An abrupt withdrawal syndrome can be precipitated by large doses of antagonists. Blood gases, pupil size and withdrawal symptoms must be monitored in determining correct dosing with narcotic antagonists.

Heroin Withdrawal

The onset of withdrawal symptoms after the last dose of heroin varies with the dose and magnitude of the habit. The symptoms of the heroin withdrawal syndrome include anxiety, yawning, lacrimation, rhinorrhea, profuse sweating, dilation of the pupils, vomiting, muscle aches and hot-and-cold flashes. Hypertension, hyperthermia and increased respiration are common. In contrast to withdrawal from sedative drugs such as alcohol and barbiturates, seizure and headache are uncommon. The duration of withdrawal symptoms is widely variable and is greatly altered by medication used in treatment. We have had a most

difficult time in gauging the narcotic requirements for patients in heroin withdrawal. We have found that the only effective way to identify the degree of withdrawal is to give a placebo in an orange flavored drink (Tang) with quinine and quinidine added to simulate the bitterness of methadone. Empirically, with house officers testing, we are able to detect a minimum of 5 mg of methadone in Tang. House staff and patients were not able to detect a difference in taste between methadone and quinidine at any dose.

By adopting a principle of testing all patients initially with a placebo, we have dramatically decreased the symptoms of withdrawal in some patients without giving any narcotics. It is generally felt that the half-life of methadone in heroin addicts is in the neighborhood of 36 hours. During severe withdrawal periods the clinical half-life may be much shorter, but in general patients are treated only once daily with methadone an initial average dose of 20 mg. Often patients will overestimate their habit in an attempt to obtain more narcotics from the physician. If tolerance to heroin is not present, giving methadone can cause severe overdose reactions. With regard to treatment for a methadone overdose, it must be emphasized that any of the narcotic antagonists must be given for a longer period in repeated doses than with heroin overdose since the half-life of methadone is longer than heroin's.

We have observed that many patients with the most severe withdrawal are very febrile and have complicating medical problems which must be searched for and treated appropriately. In our experience, infection is the most common precipitating event. Antibiotics must be reserved for the treatment of a specific infectious agent; prophylactic coverage of all heroin addicts in withdrawal would seem inappropriate and potentially dangerous. When possible, physicians should attempt to avoid intravenous infusions in these patients since this provides a ready means for illicit drug use. We allow no visitors during the entire withdrawal period, for we have sometimes seen guests administer heroin to our patients. Most of all, we should emphasize that methadone withdrawal alone is a uniformly unsuccessful way of treating the long-term problem of heroin addiction in that the vast majority of addicts who use methadone withdrawal in the hospital will return to the addiction unless the appropriate rehabilitative programs are established.

TABLE 1.—*Medical Complications of Heroin Addiction*

Increased mortality
Pulmonary complications
Hepatitis
Tetanus
Malaria
Bacterial endocarditis
Infection
Perplexing Serologic
? Necrotizing Angiitis (Citron)

Medical Complications (Table 1)

It is not surprising that the self-administration of adulterated opiates of variable concentration in large doses in an unsterile manner is frequently associated with severe medical complications. Although heroin addiction is commonly considered to be primarily a social and psychiatric problem, several interesting medical complications have become increasingly evident. However, the vast majority of patients with long-term and compulsive use of narcotics seem remarkably free of severe medical complications.

There is substantial evidence that the mortality rates for addicts are considerably higher than for age-matched controls. A definite increase in mortality rates in the United States has been described: as 16 per 1000 for addicts under 30 years of age,⁴ and 31 per 1000 for those over 30 years of age.⁵ Similar reports have come from other countries. In New York City, where careful records are kept of the total number of deaths from narcotic addiction, the absolute number of deaths has climbed steadily over the past few years. There were approximately 1000 deaths from narcotic overdose in New York City last year, and approximately 60 in San Francisco.⁵ The most feared complication of narcotic abuse, overdose, kills an estimated 1 percent of addicts in New York each year. The vast majority of addicts experience overdose at least once during the course of their drug abuse. It is clear that after the addict has been incarcerated in a hospital or jail, or otherwise kept from drug use, he returns to his previous drug habit and often disregards his abstinence-related loss of tolerance. He then may greatly overdose himself. The neophyte narcotic addict, in an attempt to imitate more experienced users, may use inordinately large amounts of nar-

*Normal Death Rate is Age 15-29, 1.2/1000 in 1970
Age 30-59, 9.6/1000 in 1970
Source: San Francisco Department of Public Health

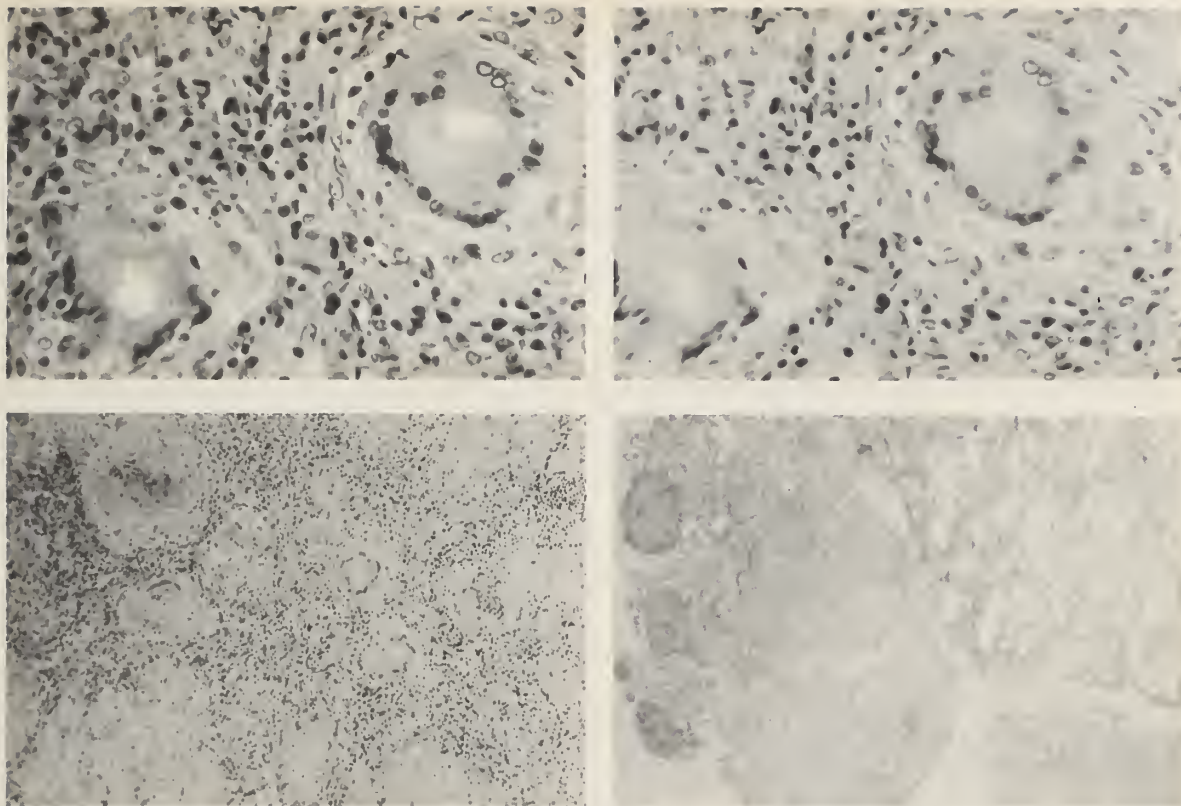


Figure 1.—Lung biopsy sections illustrating non-caseating talc granulomas with large giant cells and polarizing granules.

cotics. It is also clear that narcotic distributors, when expecting arrest or attempting to remove police informants, may pass large amounts of virtually pure heroin to unsuspecting users.

Since the addict injects himself intravenously with adulterated narcotics he may introduce particles of cotton or other filters of heroin that embolize in the lungs. This may lead to granulomas or pulmonary fibrosis and may mimic a wide variety of pulmonary infiltrates including sarcoidosis. Patients who inject paregoric and pyribenzamine (*blue velvet*) are especially liable to pulmonary hypertension and talc granuloma.

The lung reactions associated with heroin abuse are varied. Figure 1 shows sections of lung biopsy material from a young drug user who was recently evaluated at San Francisco General Hospital for progressive dyspnea and pulmonary infiltrates. She was clinically suspected of having sarcoidosis. Biopsy showed granulomas which were periodic acid Schiff negative and polarized under the microscope. These findings are characteristic of talc granuloma.

Acute pulmonary edema secondary to opiates was first described by Osler in 1880. We have recently observed four patients with acute pulmonary edema secondary to heroin overdose. Since this pulmonary edema picture was described many years before the discovery of heroin and its subsequent adulteration, it is presumed that the narcotics alone may be responsible. A recent review of many chest films of heroin addicts pointed out that pulmonary edema may occur in many patients with heroin overdose.⁶ The most common x-ray finding of this pulmonary edema is one of fluffy, ill-defined bilateral coalescent densities. Treatment with narcotic antagonists may abruptly improve the pulmonary changes. A recent paper suggested that the pathogenesis of heroin-induced pulmonary edema may be due to increased permeability of the pulmonary capillaries since some patients have normal pulmonary artery pressures and the extravasated edema fluid has a significantly greater proportion of total protein than is seen in patients with arteriosclerotic heart disease and pulmonary edema.^{7,8}

Hepatitis is one of the most frequent side effects of the chronic abuse of narcotics. It has recently been estimated that 10 to 15 percent of addicts have pronounced biochemical abnormalities consistent with acute hepatitis. Another 60 percent have distinct though far less impressive biochemical abnormalities which are usually attributed to chronic hepatitis, perhaps modified in some way by continued use of the drug.^{9,10,11} Attempts to reproduce similar abnormalities in experimental animals have been unsuccessful. Despite the abnormal liver function tests in heroin addicts, results of liver biopsy are generally unimpressive and only mild abnormalities are seen. Holmes and coworkers recently demonstrated striking hypertrophy of the smooth endoplasmic reticulum, as might be expected in persons using drugs metabolized by hepatic microsomes.¹² Although it has been said that the mortality from serum hepatitis is greater in heroin addicts, conclusive proof is lacking.

Tetanus, at least in New York City, recently has occurred mainly in heroin addicts. Subcutaneous injection ("skin popping") has been the most common route for infection with the clostridium organism. The initial symptoms are usually stiffness or pain in the neck with trismus and chest pain, and the mortality has been nearly 90 percent in the reported cases. It should be noted that a patient recovering from tetanus is not completely immune to recurrent attacks and thus should be protected from further episodes of tetanus by appropriate re-immunizations.

The largest malaria outbreak in this country in 20 years occurred recently in Bakersfield, California. This outbreak was limited entirely to narcotics users. A total of 44 patients were affected. This disease was traced to one man, returned from Vietnam, who was using narcotics. Fortunately the strain of malaria in this outbreak was *Plasmodium Vivax*, which is rarely fatal. In the marshlands of the northern central valley of California there are still *Anopheles* mosquitoes which are capable of carrying malaria if they bite an infected individual. It is both interesting and disturbing to remember that the last large outbreak of malaria in California occurred in 1952 and involved 35 Campfire girls who were bitten by mosquitoes which presumably previously had bitten a returning Korean war veteran.

Bacterial endocarditis is another serious complication of narcotic addiction. To date 93 cases

of endocarditis in narcotic addicts have been reported in the literature by 24 different authors.¹³ In New York City over 8 percent of all deaths from narcotic addiction are the result of bacterial endocarditis.¹⁴ The most commonly affected valves are the aortic and mitral valves and staphylococcus is the most frequently responsible organism. A history of underlying valvular heart disease is generally less frequent in addicts than in age-matched controls. Pulmonary manifestations of endocarditis are apparently very common. There is also an apparent increase in the frequency of tricuspid involvement, as well as infections due to *Candida* and enterococcus, in addicts although the literature is probably seriously biased toward over-reporting the unusual cases.

We have observed 10 to 20 cases of heroin-related bacterial endocarditis at the San Francisco General Hospital over the past year. Two patients had an unusual endocarditis due to *Serratia marcescens*. In this same regard, Nickerson recently reported striking increases in heat-stable opsonins of *Escherichia coli* and *Serratia marcescens* in heroin addicts.¹⁵ A recent review suggested a very high incidence of endocarditis due to streptococcal viridans in heroin addicts.¹³ This group also found that the endocarditis in heroin addicts primarily involved the left, not the right side, of the heart. However, when the lesions did occur on the right side of the heart the responsible organism was generally staphylococcus aureus. The mortality of endocarditis in heroin addicts is approximately 75 percent. Some postmortem findings in a fatal case, including a perforated aortic valve and ruptured cerebral mycotic aneurysm, are shown in Figure 2.

Since heroin in an unsterile vehicle is often injected under the skin, recurrent skin infections are frequent side effects of narcotic use. In a review of all heroin patients admitted to San Francisco General Hospital over the past year, I found that the vast majority were admitted for treatment of local infections or cellulitis due to unsterile injection procedures. Certainly cellulitis, thrombophlebitis and bacteremia are the major medical problems bringing heroin addicts to the San Francisco General Hospital.

Cherubin and Millian¹⁶ have recently emphasized the nonspecific false positive reactions of many heroin addicts to a number of common serological tests. In their study of serological reactivity of narcotic addicts who were not in hospital

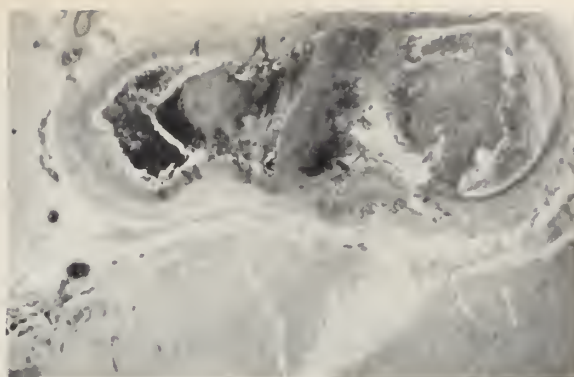


Figure 2.—Results of acute staphylococcus endocarditis in a heroin addict. *Left*, perforated aortic valve. *Right*, ruptured mycotic aneurysm.

and not in prison, they noted that nearly one quarter of them had a positive VDRL test. In those with positive VDRL tests, confirmatory tests for syphilis were positive in only 12 percent of the men and 15 percent of the women. They also found that nearly 20 percent of heroin addicts have a positive complement fixation test for lymphogranuloma venereum and 16 percent have a positive test for Q fever. Common serological tests therefore must be interpreted with caution in heroin addicts.

Sapira,¹¹ reporting from Lexington, Kentucky, emphasized a finding which we have observed repeatedly in the Detoxification Unit. Although we normally expect an elevated white blood cell count in patients withdrawing from alcohol or other drugs, we have found that the elevated leukocyte count associated with heroin withdrawal is predominantly due to an elevation in the absolute lymphocyte count, including some atypical lymphocytes and some Downey cells. Since many of the manifestations of heroin withdrawal resemble a flu-like illness—runny nose, abdominal discomfort and muscle aches—the syndrome of narcotic withdrawal may be exceedingly difficult to distinguish from a viral illness.

There are several other recently emphasized medical conditions which may occur in association with narcotic addiction. There is a striking increase in symptomatic hemorrhoids in heroin addicts, probably secondary to the constipating effects of long-term narcotic use. Several acute neurological problems have recently been observed. A crush syndrome after prolonged unconsciousness from narcotics with acute rhabdomyolysis and myoglobinuria, injection neuropathies and transverse myelitis have all occurred.

Citron^{17,18} emphasized that a necrotizing angitis which is indistinguishable from periarteritis nodosa may occur in a large number of young people with drug abuse. The patients upon whom he reported had used a multiplicity of drugs including narcotics, stimulants, hallucinogens and depressants. In some of these patients the duration of drug abuse was very short and the clinical spectrum varied from complete absence of symptoms in half the patients to multi-system manifestations including renal failure, hypotension, pulmonary edema, pancreatitis, gastrointestinal hemorrhage and hemolytic anemia. In addition to necrotizing angitis, aneurysms of medium sized arterial vessels may occur in the kidney, stomach, liver, small intestines and selected viscera. Although the initial drug abuse in most of these patients was with amphetamines, many of the patients were using narcotics. Although the medical examiner in New York City reported finding no necrotizing angitis in 1031 drug addict autopsies, the true incidence of this problem may escape pathological confirmation unless very careful autopsy studies are performed. Figure 3 shows diffuse periarteritis noted at postmortem examination of a 28-year-old heroin addict who had had repeated bouts of pancreatitis and died suddenly after (apparently) intravenous use of heroin in the hospital.

In conclusion, it is clear to those of us dealing with these patients that narcotic addiction is a serious and growing problem that will probably be increasing in magnitude rather than decreasing in the near future. Nevertheless, only about 15 percent of medical schools have in their curricula specific teaching programs concerning the management of drug abuse and alcoholism. The

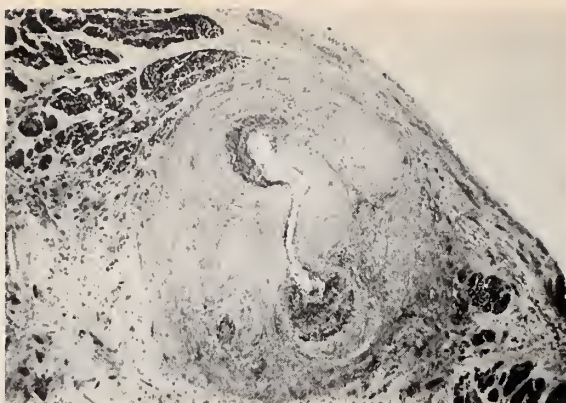


Figure 3.—Myocardial vessel illustrating a striking clinically unrecognized periarteritis nodosa-like lesion.

old ways of dealing with narcotic addiction, including stringent laws and police enforcement, have been a failure from the point of view of rehabilitating the young drug offenders and correcting their illness. Imprisonment has done little but propagate addiction. As physicians, we can successfully treat the withdrawal symptoms and the development of tolerance in addiction, but we are still left with the primary behavioral problem for which little treatment and insight is currently available. It is, however, clear that the pendulum of responsibility for the care of these patients is now swinging to the medical profession rather than the law enforcement agencies. We must therefore strive to find solutions to these problems.

"SILENT" BLEEDING FROM INJECTION WOUNDS

A fair number of patients on heparin bleed because of trauma caused by us, . . . The most common problem has been giving intramuscular medications to these patients. Giving the medication with a large needle into the gluteal area has been a formidable hazard; several patients locally have bled to the point of requiring massive transfusion therapy. Unfortunately these patients often bleed into an area that's clinically silent (because the bleeding may be deep). It may not penetrate to the skin and cause surface ecchymoses. It may go down as far as below the knee and upward into the retroperitoneal area, and only after several days when the blood does surface to the skin is the clinician aware of this. One of the points to be made here is that if the patient is on heparin, it's wise to monitor the hematocrit every two or three days because this will be the first way of picking up unsuspected bleeding.

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TRADE AND GENERIC NAMES OF DRUGS

<i>Amytal</i> ®amobarbital
<i>Nembutal</i> ®pentobarbital
<i>Seconal</i> ®secobarbital
<i>Nalline</i> ®nalorphine
<i>Lorfan</i> ®levallorphan tartrate

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College Health Services

THE QUESTION "What is the world coming to?" is ageless, and for the physician looking to the future of medical care and health problems there is one answer among many that is too easily forgotten in the jungle of comprehensive health planning, discussions of health delivery systems and problems of medical economics. Quite simply one thing the world is coming to is the youth of today. The young adult on the campuses of our colleges and universities is the client or patient for health care in the future. How does he or she view medical care? How does he or she consider the role of the physician? Where will he or she seek health care in the future?

The discussion by E. D. Lovett, M.D., elsewhere in this journal presents a challenge to the medical profession with the opportunity to influence the answers to the above hypothetical questions.

There is a very old axiom that states that if there is an unmet need or problem in the field of health for which trained, experienced, expert, competent and available health professionals do not provide the answer, then inexperienced, untrained, non-professional persons will step forward into action rapidly and take on the responsibility for leadership. Stating this another way: If the health professions do not assume the role of leadership in the area of health, somebody else will.

Experience with the health problems of college and university campuses throughout the nation and the state gives many examples where the operation of this axiom can explain the presence in a leadership position of persons from other than the health professions who are doing ineffective and less than satisfactory jobs. Some recently encountered examples are:

A medical history form and physical examination report to be completed by the private physician is designed and distributed by the regis-

trar of a large university campus who then receives the form as completed by the candidate and his physician for "evaluation" by clerks in the registrar's office.

An intercollegiate athlete with a single kidney is advised not to play football by his family physician. The nurse in the health service of the athlete's college advises the student to this effect and the president of the college over-rides the nurse's decision.

A student-body president on a college campus plans a critical survey of the health service program on his campus and turns to a national association of college deans for advice on how to evaluate a health program.

A nurse, alone in a college health program, realizing her dangerous medico-legal position, seeks the appointment of a physician to provide written direction and available consultative assistance. She is informed by the college administration that her immediate supervisor is the dean of students and that such is supervision enough.

The accreditation committee for a regional organization of educational institutions reports on a college health program that "a nurse is in attendance one day a week," and that, "in addition to handling the normal traffic of ill students she investigates dormitory conditions, sanitation, safety, and is currently engaged in the health education program." This college was given full accreditation and a special note of approval for "an outstanding health program" was included.

The personnel office on a community campus requests the nurse in the health service to prepare a proposal and program for occupational medicine involving employees of the college. The nurse's immediate supervisor, a dean in the campus administration, instructs the nurse to turn the problem back to the personnel office. The personnel officer then develops a plan based on his experience as a personnel officer and as a former officer in the Supply Corps of the United States Navy.

We need not pursue these examples any further and the picture is all too clear to health professionals working in higher education in California.

In 1830 a most perceptive young Frenchman, Alexis de Tocqueville, made the observation that Americans established associations to do a variety of very important things. He said, "Wherever at the head of some new undertaking you see the government in France or a man of rank in England, in the United States you will be sure to find an association." It is apparent that in recent years in the United States there has been a trend away from this. More and more we are inviting the government to take on some of the activities of our independent associations, which seem unable to recognize their own potential for significant accomplishment.

The physicians of California are given the challenge by Dr. Lovett of unmet needs and unsolved problems of many of our California institutions of higher education. He quite properly emphasizes that the greatest impact can be provided by personal involvement of individual physicians in their local colleges and universities.

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Coronary Arteriography: Where? When?

THE PAPER IN THIS ISSUE by Selzer, Anderson and March, "Indications for Coronary Arteriography," presents a contemporary summary of the risks and benefits of coronary arteriography. The authors have examined the risks in relation to the experience of the diagnostic laboratory. They also have raised pertinent questions about the widespread application of coronary arteriography when this is done outside the context of sophisticated radiological and physiological interpretation and a surgical team evaluating the collective results of what is at present experimental surgery.

The standards for laboratories and hospitals performing diagnostic hemodynamic and angiographic studies have evolved from numerous publications and the recommendations of the American Heart Association. These reports have pointed out the higher incidence of complica-

tions when such procedures are done infrequently. The information presented by Selzer et al again emphasizes the significantly greater morbidity and mortality in laboratories performing a limited number of diagnostic studies.

Regrettably, many community hospitals have generated hemodynamic and angiographic laboratories, as well as open-heart surgery teams, which must be regarded more as status symbols than services required because of a significant case load and the lack of alternative diagnostic and surgical resources.

The laboratory that performs few studies operates less safely for a number of reasons. Procedures are apt to be protracted because of the inexperience of the technical personnel. There may be equipment faults because the instruments have lain fallow for several weeks, or because the size of the operation does not justify employment of a technician to test and troubleshoot the electronic systems. The isolated diagnostic laboratory that has no supporting surgical team operates at a particularly unsafe disadvantage because occasional complications during study require immediate surgical intervention.

The lower complication rate of laboratories with high case loads is not necessarily related to the level of training of the persons performing the procedures, but is probably more directly the result of repetitive practice afforded by a large number of studies. The complication rate at the University of Oregon Medical School, for example, is as low as that of other medical centers studying a large number of patients, although most of the procedures are done by trainees under staff supervision.

If the risk of coronary arteriography is to be minimized, the procedures should be done in a laboratory that performs a number of studies sufficient to maintain the technical facility of the operator and his assistants. This probably requires three or more angiographic studies per week and a collateral open-heart surgery load of at least two cases weekly.

The development of coronary arteriographic techniques and the successful results of revascularization and coronary bypass surgery have caused enormous pressure on medical centers to perform diagnostic studies and surgery. Examples of immediate symptomatic improvement after aortocoronary bypass surgery are quite impressive, but the rate of surgical failure is still

significant, and the collective evidence is thus far inadequate to determine the effect on survival and prevention of myocardial infarction. In view of these uncertainties, it is particularly illogical to consider coronary arteriography in all patients with coronary artery disease in order to screen for operability.

Selzer et al state indications for coronary arteriography which are appropriate to current diagnostic and surgical extrapolations. There is no doubt that arteriography discriminates coronary arteriosclerosis in most instances in which it is present, and provides precise quantitation of the disease when the diagnosis is in question, or when the disability under medical treatment is sufficient to warrant surgical consideration. Coronary visualization before valvular surgery in older patients has contributed to more accurate assessment of the risk and has aided the surgical planning. And even though the final results are unknown, the mortality and morbidity risks after myocardial infarction in young patients are high enough to justify arteriography in evaluation for coronary surgical procedures.

No doubt the indications defined by Selzer et al will change along with experience and the wider collection of objective data evaluating coronary surgery. Until many questions are answered, these would seem to be reasonable current guidelines.

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Medical Education in Transformation

MOST PRACTICING PHYSICIANS are aware that profound changes are taking place in medical education, but comparatively few must know the extent of these changes or be aware that they are

occurring with relatively little understanding on the part of anyone as to where they are likely to lead. There can be little doubt that medical education is once again undergoing transformation, only this time apparently without any such clear purpose as that which followed the Flexner Report in 1910.

What is occurring is a reflection of both the character of the times and of enormous expansion in the amount of medical knowledge. Many new factors have come into play. There is a new positive emphasis on health and avoidance of disease which cannot but influence medical education. There is much more attention being given to cultural backgrounds of both students and patients, to overcoming "racism" in medical school and medical care, and to what is called "affirmative action" which seeks to ensure that the population of the medical school student-body more nearly reflects the cultural composition of the population to be served in practice. The idea that education should satisfy one's own personal needs rather than fulfill anyone else's prescribed norms, something generally accepted at the college level, is now making its appearance in medical education.

This is beginning to challenge and even erode the idea that there is a basic body of professional knowledge which all physicians must have learned and which has been a principal basis for the trust his patients and others place in him when they seek his advice. Active student participation in administrative decision-making at all levels of the educational process is the order of the day in medical schools, and this can be time consuming. Medical school curricula have been changing dramatically in an effort to respond to demands for a shorter time in training and greater flexibility in scholarship and content. And not the least of these new factors transforming medical education is the government, which by both accident and design is exercising a most profound influence for better or for worse.

The evidence leaves no doubt that a very basic transformation in medical education is well under way. But the evidence also suggests that what is happening is dangerously lacking in clear purpose or direction. For example, there is no clear consensus as to just what medical education in its new form is to accomplish. In fact there is no clear perception of just what tomorrow's physician will be doing and thus for what

he should be prepared. Lacking clear direction, the process of transformation is rather haphazard, with its activities somewhat resembling multidirectional Brownian movement. The medical educators are seeking ways to improve the transfer of a growing body of medical knowledge to students of whatever category. Students aspire to a measure of control over what they will study and how they will study it. Government tries to influence the whole process by allocating funds and resources to such activities in research, education or patient care as are in accordance with whatever it considers to be in the national interest at the moment. And notably lacking in all this is any really significant input from physicians and others with substantial expertise and experience with the real-world problems of rendering health care.

The practicing medical profession has always had an important stake and an important responsibility in medical education. In recent years this responsibility has been increasingly subsumed by others. But medical education is primarily for real-world medical practice and this is where the practicing profession has unexcelled experience and competence, and this is why experienced practicing physicians should participate more closely in the various decision-making processes at all levels.

This lack of significant input from the practicing profession into the transformation of medical education is something which could and should be remedied by both medical schools and practicing physicians. Once again California can lead the way.

The Health Care Team

THE HEALTH CARE TEAM has often been discussed just as though it were something tangible and definable. One is reminded of the fable "The Emperor's New Clothes." Though the emperor actually had nothing on at all, his new "clothes" were highly touted by his courtiers and lauded in the palace publicity. Consequently, they were praised and admired by his subjects, each one

thinking the others could see something he could not. Finally an innocent child announced in a loud voice that the emperor had no clothes.

Perhaps there is a lesson in this. Is there any real substance to the health care team everyone has been talking about? If there is, it has certainly been very difficult to define.

Since there has been all this discussion of the health care team, it might be useful to attempt a definition. The American Medical Association calls *health* "a state of physical and mental well-being," while the World Health Organization goes further and calls it "a state of complete physical, mental and social well-being and not merely the absence of disease." *Team* has been defined by Webster as "a number of persons associated in any work." The health team might then be defined as "a number of persons associated together" to bring about "a state of physical and mental well-being" (AMA definition) or "a state of complete physical, mental and social well-being, and not merely the absence of disease" (WHO definition). Defined in this way, the health care team is seen to be composed of the totality of health care personnel dealing with the totality of health care problems in the broadest conception of both these terms. Maybe this is what *the* health care team really is, and if so then much of the discussion and much of the touting has been directed toward a non-specific generality.

It would seem, therefore, that the appropriate subject matter for discussion is not *the* health care team. *Health care teams* appear to be a far more manageable concept. These are composed of a selected segment of the totality of health care personnel who are organized to perform some specified task within the totality of health care. In this more limited concept health care teams can be described and studied. Such teams will usually be ad hoc in their purpose, their life expectancy may be relatively short, and thus they may be expected to assemble and disassemble frequently.

In this conception health teams have been with us a long time. Such teams may involve physicians, allied professional and non-professional personnel who work together to care for a particular patient, to eradicate malaria from a specific geographic area, to perform a complex surgical procedure, to do a research project in health science, to improve the level of health care in a

poverty area, or to accomplish any one of a myriad of other purposes. The question of where the responsibility lies and who is captain of these teams is arising with increasing frequency. In the operating room it is clear enough. The surgeon has the responsibility and is the acknowledged captain. But in other situations it is not so clear. The team leader may serve more as the chairman of a committee or group and may not even be a physician, even though physicians are part of the team.

Physicians must learn to work smoothly and effectively in these various team situations. They

must come to understand their own capabilities and limitations and those of the other kinds of professional specialists who serve on them. They should study more of team dynamics, and develop the skills which are necessary to be an effective team leader, coordinator, participating member or technical advisor, as the case may warrant. For the foreseeable future medical and health care are certain to become increasingly a matter of team effort.

The health team may have no clothes, but health teams do! The physician must fit himself into them.

TSH IN THYROID CANCER

It does appear that there are high levels of thyroid-stimulating hormone (TSH) in thyroid cancer. What is the significance of this from the therapeutic standpoint?

About 30 to 50 percent of thyroid cancers are TSH-dependent in the sense that you can make them grow if you give the patient TSH or allow him to remain hypothyroid after surgery. This has been demonstrated in a number of ways, including the rapid growth of the tumor or metastases in a myxedematous state. Also we sometimes give injections of TSH to encourage a tumor to take up radio-iodine so it can be treated. There have been a number of reports of patients in whom metastases grew remarkably during the periods of TSH stimulation. . . . One can slow down, arrest, or even (rarely) cause regression of tumor by suppressing endogenous TSH.

The important thing to remember is that it takes large doses of thyroxine to adequately suppress endogenous TSH in patients with thyroid cancer. I would encourage you in treating postoperative patients with thyroid cancer to give large doses of thyroxine, as much as can be tolerated. From the theoretical standpoint this will have the best results, and from the practical standpoint as well; I personally have seen a number of patients in whom giving larger doses of thyroxine than commonly used sometimes produced dramatic results in arresting or even reversing tumor growth.

Normally one sort of fools around with about 0.1 to 0.2 mg. . . . These doses are really quite inadequate to suppress the pituitary in patients with thyroid cancer. One should give a minimum of 0.3 to 0.4 mg of thyroxine and more if the patient can tolerate it. . . . In almost all patients I would push it until they start showing some evidence of getting thyroxine. Don't make them toxic, but just this side of toxic.

—JEROLD M. LOWENSTEIN, M.D., San Francisco
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CASE REPORTS

Malaria Transmission Among Narcotic Addicts

A Report of Ten Cases and Review of the Literature

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THE TRANSMISSION OF MALARIA between human hosts without a mosquito vector was first reported in 1884 by Gerhardt,¹ and such transmission is now well recognized; intentional malaria infestation by the parenteral route comprises a well known era in medicine, accidental transmission by whole blood transfusion is well documented,^{2,3} and transplacental malaria has been reported.⁴ The first cases of accidental transmission between narcotic addicts were reported in 1929 by Biggam⁵ who reported ten cases of falciparum malaria contracted by the sharing of needles by heroin users in Cairo. Between 1933 and the early 1940's several reports of additional cases of malaria among addicts were reported. No such cases were reported after 1942.

Submitted March 9, 1971.

Reprint requests to: Kern County General Hospital, 1830 Flower Street, Bakersfield, Ca. 93305 (Dr. R. L. Bick).

Recently we have observed ten cases of malaria due to the common use of needles by heroin addicts. None of the persons involved had been in foreign countries, all had been using heroin for at least one year, and all had injected heroin in the six weeks before seeking medical advice because of malarial symptoms. Five of these ten cases are presented here.

Reports of Cases

Case 1. A 25-year-old Mexican man came to Kern General Hospital with complaint of chills and fever accompanied by diaphoresis for five weeks. Initial evaluation led to an admitting impression of serum hepatitis. The patient was noted to have hepatosplenomegaly and scleral icterus. A test for Australia antigen was positive. However, routine examination of the peripheral blood smear revealed Plasmodium vivax parasites. The patient said he had been using heroin for a year and had last injected it two weeks before admission.

Case 2. A 21-year-old Caucasian man was seen two days after the patient in Case 1 with complaint of weight loss, recurrent chills and fever 40° C (104° F) occurring at 6:00 p.m. every two days for the preceding five weeks. On preliminary examination scleral icterus, temperature of 40.5° C (105° F) and splenomegaly were noted. Initial impression was fever of unknown origin. Examination of peripheral blood showed ring forms of P. vivax. The patient last used heroin two days before admission. He had positive reaction for Australia antigen.

Case 3. A 24-year-old Mexican man had chills and fever for six weeks while being held by authorities for the use and sale of heroin. He was brought to Kern General Hospital. Mild scleral icterus, temperature of 39.5° C (103° F) and hepatosplenomegaly were noted. A smear of peripheral blood was immediately obtained

and *P. vivax* was found. The patient had last taken heroin eight weeks before hospital admission. Australia antigen studies were negative.

Case 4. The patient, a 19-year-old sister of the patient in Case 3, admitted sharing needles with her brother, and she also had had chills and fever for the past month but had not sought medical attention. Examination of the peripheral blood also revealed *P. vivax* parasites and she was admitted to the hospital. No icterus was noted but the spleen and the liver were enlarged. A test for Australia antigen was negative.

Case 5. The 20-year-old wife of the patient in Case 3 wrote to her husband during his stay in hospital, complaining to him that she had been sick with chills and fever. Since she was living 200 miles away at the time, a phone call was made to her and she was asked to report to her local county hospital. Instead, she came to an office of the Kern County Health Department and from there was transported to the hospital. She also was found to have temperature of 40° C (104° F) and significant hepatosplenomegaly. Examination of the peripheral blood revealed vivax malaria. Australia antigen studies were negative.

Discussion

Since the previously mentioned ten cases, additional cases are being found in our community. To date all such cases have been among heroin addicts and all have been due to *P. vivax*. Three of the cases here reported were definitely related—those in the man, wife and sister who shared their needles. The other patients have not admitted to a clear interrelating path of infection. The average time of onset of symptoms was two to three weeks following the suspected exposure and most of the patients were symptomatic for five to six weeks before seeking medical attention. In most of the cases the diagnosis was made by noting parasites on a routine Wright-stained peripheral smear obtained following a suggestive history. In all cases the parasites were first noted by a laboratory technician and the observation later confirmed by a pathologist.

The patients were all treated with the following regimen: chloroquin hydrochloride (Aralen® hydrochloride), 1 gram by mouth initially followed by 500 mg in six hours, then 500 mg every morning for two days. Primaquin phos-

phate (Primaquin® phosphate), the tissue antimalarial, was not used because the tissue phase of infectivity in vivax malaria is avoided if transmission is by other than the mosquito vector.

The ten cases came to light in only ten days of investigation, and we expect this problem to increase in our addict population before all carriers are detected and treated.

A review of the literature turned up reports of a total of 522 cases of malarial transfer by needles. This total came from ten separate reports,⁶⁻¹⁵ with the largest series from New York City and from Chicago in the early 1930's. These were predominantly cases of falciparum malaria. When all world cases were surveyed, the same trend was noted: 38 (7 percent) of all cases were caused by *P. vivax*, 271 (52 percent) by *P. falciparum*, six cases (1 percent) by *P. malariae*, and 207 (40 percent) by unspecified species. We were unable to find any reports of *P. ovale* transmission by this route.

Because of the malignant nature of *P. falciparum*, we feel the high relative incidence of reports of this form of the disease in this population might be due to the necessity of seeking medical attention, as persons with other forms of the disease might be inclined to ignore their milder symptoms. The mortality noted in the review of 522 cases was higher¹⁶ than would be expected in populations acquiring the same disease through natural vectors. This again may be partly attributable to the high incidence of falciparum malaria in the cases reported.

No such cases were reported during this country's involvement in Korea, and it is quite surprising that no previous cases of this nature have been reported since military operations in Southeast Asia began more than ten years ago. Our series is most likely related to a Vietnam returnee. In all of our cases *P. vivax* was the infecting organism. Eighty percent of the malaria among soldiers in Vietnam is due to *P. falciparum*, but 80 percent of malaria in soldiers returning to the continental United States is due to *P. vivax* because of the persistent asymptomatic extraerythrocytic stage.¹⁷ Almost 4,000 cases of malaria were documented among servicemen returned from Vietnam in 1969.¹⁸

Malaria, like serum hepatitis, may reach significant proportions in this era of prevalent drug abuse. In this regard we have found tests for

Australia antigen helpful in detecting patients who may have both diseases, as the clinical manifestations of one might easily mask those of the other. Malaria among narcotic addicts appears to be a renewed clinical problem of which physicians should be aware, especially in addicts who might present with bizarre symptoms or with fever of underdetermined cause.

Summary

Vivax malaria was observed in ten heroin addicts who admitted to the sharing of needles. None had traveled outside the United States. It was suspected that these cases are related to a Vietnam returnee, although this was not definitely established. All cases were diagnosed by routine peripheral smears. In view of our military involvement in Vietnam and the prevalent use of drugs in the civilian population being joined by returning servicemen, clinicians should be alerted to the problem.

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Duodenocolic Fistula

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A NON-MALIGNANT CONNECTION between the duodenum and the colon is a rare condition of diverse causes. The anatomic proximity of the two structures allows disease or injury of either to result in fistula formation, occasionally in combination with a third structure, the appendix or the gallbladder. The unique and the rather distinguishing clinical features of this condition have led to the report of the present case and the review of other reports.

Incidence

Despite the anatomic nearness of the duodenum and the colon, fistula formation is quite rare. In most of the cases in which it does occur it is due to malignant disease (Medhurst, 1956).¹ Non-malignant fistula was reported only 27 times between 1863, when Sanderson reported the first such case, and 1966 when Brindle and Kane² added two cases and surveyed the literature to that time. In the same year, another case was reported, by Trickey and Dorling.³ The present case is the only one reported since. Undoubtedly there are many cases not reported, yet the condition is so rare that few surgeons have seen one.

Etiology

The most common cause of this fistula is duodenal ulcer disease (Table 1). The fistula may develop insidiously from direct extension of the ulcer crater, or it may occur secondary to a perforation and abscess formation, as reported by Starzl (1959).⁴ Foreign body penetration was reported by Rosenqvist (1955)⁵ and Trickey (1966).³ Tuberculosis involving abdominal lymph nodes with caseous necrosis and fistula formation was a factor in five instances. Fistula secondary to ulcerative colitis has been reported twice, and to regional enteritis twice—somewhat surprising since fistulas elsewhere in the gastro-

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TABLE 1.—*Causes of Benign Duodenocolic Fistula*

Duodenal Ulcer
Duodenal Diverticulitis
Tuberculosis
Typhoid Fever
Appendicitis
Cholecystitis
Foreign Body
Trauma
Ulcerative Colitis
Regional Enteritis

intestinal tract are not uncommon with these diseases. Cholecystitis caused a fistula in a case reported by Neville (1954).⁶ Other case reports indict typhoid ulcer, duodenal diverticulitis and trauma.

Appendicitis as the cause of duodenoappendicolic fistula has been reported twice previously. Clayton and Thornton described a patient with chronic symptoms of acute appendicitis who was treated with aspirin and hot packs.⁷ After six days of stormy illness, he recovered but had continuing diarrhea. Later, at operation, he was found to have a fistula between the duodenum and the cecum, adjacent to the appendix base, and an open appendix. A similar case was reported by Marinaccio et al in 1953 and cited by Starzl in 1959.⁴

Report of a Case

A 40-year-old Filipino with bronchial asthma had onset of diarrhea which was difficult to control about four months before admission to hospital. He noted postprandial cramping in the upper abdomen and postprandial diarrhea. Stool studies for ova and parasites, fat, undigested protein and enteropathogens were negative. Barium enema demonstrated filling of the small intestine, but the presence of a fistula was not determined. The diarrhea and abdominal pain ceased spontaneously. Then the asthma worsened so much that the patient was admitted to hospital for that reason. Steroids were given with satisfactory response and he was discharged. Three days later he was readmitted with nausea, vomiting, abdominal pain, abdominal distension and recurrence of diarrhea. Abdominal x-ray studies showed abnormalities interpreted as partial small bowel obstruction or severe ileus.

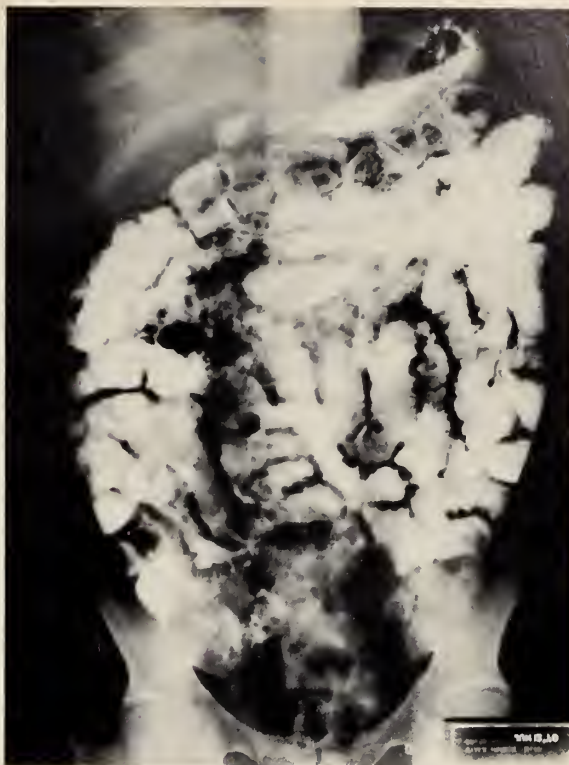


Figure 1.—Barium enema study shows distal small intestine is edematous and somewhat amorphous. It was noted to be rigid at fluoroscopy.

On physical examination the patient appeared chronically ill and there was evidence of loss of weight. The abdomen was distended and doughy to palpation, with tenderness in the right upper quadrant. The temperature was 38.9°C (102.0°F). The blood count was bizarre: Leukocytes numbered 6,000 per cu mm with a differential of 6 percent neutrophils, 45 percent non-segmented neutrophils, 25 percent lymphocytes and 24 percent monocytes. The hematocrit was 45. Three days later leukocytes were 6,200 but the monocytosis had disappeared and the neutrophils had risen to 30 percent and the non-segmented neutrophils had dropped to 34 percent. Acid-fast sputum stains were negative. Results of stool examinations were within normal limits.

The patient was treated with intravenous fluids only for three days while investigation was pursued. He remained febrile during that time. A presumptive diagnosis of intestinal tuberculosis was made, and treatment with streptomycin, para-aminosalicylic acid (PAS) and isonicotinic

acid hydrazide (INH) was begun. Within 24 hours fever abated and it did not recur.

Barium enema studies again showed diffuse rapid filling of the entire small intestine, and a diagnosis of a fistula was entertained. An upper gastrointestinal series and small bowel follow-through then demonstrated a fistula between the third portion of the duodenum and the right side of the colon. The distal half of the small intestine was smudged and edematous, appeared chalky and amorphous, and the wall of the ileum was of rigid configuration. (Figure 1). The interpretation was regional enteritis. Alimentation was gradually increased with no recurrence of diarrhea. Antituberculosis drugs were continued and after ten days of rest and food the patient was operated upon.

Operative Findings

Except for white coloration and thickening of the inferior mesenteric surface, no abnormalities were noted in the free peritoneal cavity. The cecum was normal except that the appendix was not visible. The hepatic flexure was released and the colon was freed and moved to the left. The appendix, which lay behind the cecum, was connected by a fistula to both the duodenum and the cecum. Immediately adjacent to that fistula was a second, separate duodenocecal fistula. There were no signs of inflammation in the retroperitoneal tissues. Operative repair consisted of simple division of the fistulas and two-layer closure of the duodenum and colon. The appendix was removed. Healing and recovery were uneventful. The patient gained eight pounds in the first three weeks after operation and remained well, without diarrhea, thereafter.

Clinical Presentation

The symptoms of duodenocolic fistula (Table 2) are similar in all cases regardless of etiologic factors, although a primary disease may add other signs and symptoms to those of this condition. All patients lose weight and nearly all will have diarrhea. Pain—vague upper quadrant aching or severe upper quadrant or central pain with radiation to the back—is present in 60 percent of cases, and in 50 percent there are foul eructations and vomiting. Barium contrast studies will almost always demonstrate the fistula. Although

TABLE 2.—*Clinical Symptoms of Duodenocolic Fistula*

Weight Loss
Diarrhea
Abdominal Pain
Vomiting (Feculent)
Foul Eructations

the barium enema is said to be the better test, in the present case the upper gastrointestinal series was superior. Both studies should be done as part of the preoperative investigation.

Pathophysiology

Diarrhea and weight loss may be secondary to the mechanical short-circuiting of the small intestine. However, the diarrhea is seldom profuse, or "total," and frequently is intermittent, suggesting that some food travels through the intestine in normal fashion. There may be impaired function of this intestine due to "contamination" by colon bacteria, causing jejunitis with resulting decrease in absorption of vitamins and proteins and other nutrients. Indeed, most of the fistulas described are 1 cm or less in diameter. In the present case diarrhea ceased completely when streptomycin was given as a preoperative measure (because of the possibility of tuberculosis). In addition, the x-ray studies of the small intestine showed edema and flocculation (Figure 1) that were interpreted by the radiologist as diffuse inflammation. It was for this reason that our preoperative diagnosis was regional ileitis. If the symptoms are caused by this fecal contamination, then antibiotic treatment should abate the malnutrition and help overcome some of the nutritional deficiencies. In a poor risk patient, long-term nonabsorbable antibiotics might even be selected as preferential treatment.

Treatment

The above considerations notwithstanding, surgical treatment will generally be selected. The specific operation in each case will be determined by the status of the tissues and the underlying etiologic factors. Obviously, simple division and closure of a fistula is preferable if possible, but if there is inflammatory tissue or an active abscess the surgeon will have to decide whether it is best to use drainage, resection, serosal patching or

some other measure. The surgeon also must consider the cause of the fistula, since the primary process may require definitive surgical treatment. Such treatment may be indicated at the time of fistula division (for example, total colectomy for ulcerative colitis) or at a secondary laparotomy (for example, gastrectomy or vagotomy or both for duodenal ulcer).

Preoperative restoration of vitamins, minerals, electrolytes, blood, protein, and blood volume is essential to a safe operation and an uncomplicated postoperative course. The degree to which this restoration can be accomplished will depend on the severity of the process, the condition of the patient and the response to treatment. As in gastrointestinal fistula of other kinds, no time should be lost in nonhelpful treatment when division of the fistula per se is required to reverse pathophysiologic changes.

Summary

Duodenocolic fistula not associated with cancer is a rare condition of diverse cause. A case secondary to appendicitis with a resulting duodenocolic fistula is reported. Certain aspects of this case suggest that the cardinal findings of diarrhea and weight loss are more likely due to colon bacterial contamination of the small intestine than to mechanical by-pass through the fistula. Treatment of duodenocolic fistulas is governed by a variety of factors.

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Retrieval of Catheter Fragments

Report of Two Cases

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THE RETRIEVAL OF BROKEN POLYETHYLENE catheters, guide wires and pacemaker catheters from various sites in the cardiovascular system has recently received increasing attention.¹⁻¹³ It is clear that many, if not most, of these fragments can be retrieved by non-surgical means.^{4,8-13} Several methods have been described in the literature for such retrieval.^{8,9,12} During the past year we have had opportunity to remove broken pieces of catheters from two patients, utilizing variations of existing techniques. The purpose of this report is to emphasize that in all such incidents an attempt first should be made to remove the catheter by a non-surgical method, with operation held in reserve.

Case 1. A 20-year-old white woman was admitted to hospital following an overdose of tranquilizers. When first seen, she was semicomatose and responded only to deep pain. A medium-Intracath®* was inserted into the left median basilic vein. Within a half hour the patient became restless and agitated, and after attempts to calm her succeeded it was noted that the intravenous catheter had been dislodged and was several inches shorter than when inserted. An x-ray film of the chest showed the catheter fragment (which was radio-opaque) to be lodged in the apex of the right ventricle and extended to the right lateral wall of the right atrium. The patient was taken to the cardiac catheterization laboratory, where a No. 7 Goodale-Lubin catheter with an 0.035-inch Teflon guide

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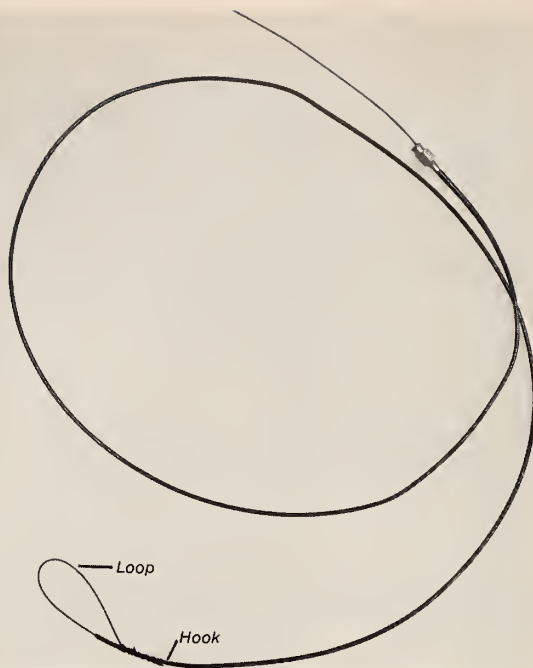


Figure 1.—No. 7 Goodale-Lubin catheter with a .035 inch guide wire with a 20 cm flexible end. See text for details.

wire, the end of which was tied back with 4-0 silk to form a loop (Figure 1), was introduced under fluoroscopic visualization via a cutdown in the right antecubital fossa. The guide wire had a 20 cm flexible end which enabled us to change the loop size easily. Attempts to surround the catheter fragment with a loop of varying size was unsuccessful, due apparently to the wedging of the fragment between the walls of the right atrium and right ventricle. The loop was then retracted and the tied end of the guide wire was used as a hook and advanced carefully into the right ventricle. The fragment was snared and was removed slowly as it doubled over on itself. Total fluoroscopy time was seven minutes.

Case 2. An 8-year-old boy underwent percutaneous femoral venous catheterization for the diagnosis of cyanotic congenital heart disease. The patient was thought to have a truncus arteriosus by clinical, radiographic and electrocardiographic determinations. During the catheterization through the femoral vein sheath, some resistance was encountered in the introduction of one of the catheters. When fluoroscopy was again begun, it was immediately appreciated that the sheath had become torn from its attachment and was lodged in the inferior vena cava,

at the level of the first lumbar vertebra. A cut-down was performed, with exposure of the femoral vein, and a No. 4 Fogarty venous thrombectomy catheter was introduced and inflated in a position proximal to the sheath fragment. A No. 7 Lehman catheter with a doubled-over 0.025 inch flexible guide wire was introduced into the vein and the sheath was snared with the loop.

Comments

While the incidence of catheter embolism from broken intravenous catheters and guide-wires is unknown, it seems likely that it is greater than has been generally reported. The complications of sepsis, thrombosis, perforation, and endocarditis produced by catheters or catheter fragments have been well documented in the literature.^{5,6,13} In addition to these, arterial embolism was seen with the accident which occurred in Case 2 herein reported, and the outcome with this patient suggests that it is well first to try removing the catheter fragments without resort to thoracotomy.

The techniques used in the two patients reported are variations of previously reported techniques. In Case 1 the problem was particularly difficult in that both ends of the catheter fragment lodged against the cardiac wall. Attempts to remove this fragment with a standard loop failed. A hook-like device utilizing a flexible-tip guide-wire which could be passed through a catheter and tied back at the tip of the catheter was designed (Figure 1). This device was then passed intravenously with the loop partially extended without causing discomfort to the patient. Once the fragment was caught in the hook, by gentle manipulation and turning it was removed from the heart without complications. Potentially, however, this technique is dangerous and should be performed with surgical standby. In Case 2 because there was danger of atrial embolization of the fragment a Fogarty balloon catheter was passed and inflated proximal to the catheter fragment. The fragment was then easily snared with a conventional "loop-type" technique.

Other patients at Stanford have had catheter fragments removed with the doubled-over guide-catheter arrangement. The two reported cases represent modifications of the usual technique. Although it will not always be possible to avoid

thoracotomy, it seems that attempts to remove catheter fragments will frequently be successful in a cardiac catheterization laboratory utilizing a hook-type device or its modification. In our experience, this technique has been successful in all cases in which it has been tried. For general purposes, various catheter arrangements with doubled-over guide-wires or instruments described by Ranniger seem to be preferable.⁹

Summary

Two cases are reported in which fragments of catheters were successfully removed from the venous system by variations in existing techniques. It is emphasized that such attempts should be made and that they be carried out in a cardiac catheterization laboratory as soon as the patient can be transported there.

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BE SKEPTICAL OF THE VMA TEST

Never operate on a patient with suspected pheochromocytoma on the basis of one positive vanilylmandelic acid (VMA) test, especially if it's one of the new quickie screening tests rather than a specific test. Also remember that certain drugs, especially methyl dopa (Aldomet®) or monoamine oxidase inhibitors, can decrease the VMA value, but increase the metanephrine value (another test for pheochromocytoma). Whenever possible, patients should abstain from all medicines, especially nose drops and bronchodilators, for 48 hours before testing; fruit, coffee, and vanilyl-containing products should also be stopped. This is especially true with the screening tests.

You should try to get at least two positive tests. If you use a broad screening test, then follow it up with a more specific test, at another laboratory if necessary, or make it more specific with metanephrine. . . .

If your tests are negative on a prime suspect, don't give up. The disadvantage of all pressor amine tests is that the tumor may not be secreting continually; in about 10 percent of patients you may continue to get negative despite the presence of a pheochromocytoma. Our last patient had four negative VMA's before he finally had a positive during a spell in the hospital and then a positive metanephrine after that.

—LLOYD D. FLINT, M.D., Boston
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LETTERS *to the Editor*

A Synergistic Danger In Ketamine and Innovar®

To the Editor: In recent months it has become common practice for physicians to utilize either ketamine (Ketalar®) (Ketaject®) or Innovar®, a fentanyl-droperidol preparation, as either the anesthetic adjunct or the only agent in anesthetizing young patients for short-term procedures.

The advantages of this technique are obvious; not so obvious are some lethal disadvantages. Both ketamine and Innovar potentiate the effect of barbiturates and narcotics. Generally, a physician could be expected to rule out the presence of such drugs prior to surgery. The current social scene has changed this. Because of the onus of drug abuse many youths refuse to admit to recent drug use. Some who have brought their own supply to the hospital with them and have taken drugs the morning prior to surgery will staunchly deny that they are drug users. With heroin the problem may be self-evident. Again, depending on the carefulness of the youth, it may not. Because of this the physicians may be lulled into believing their patients are drug free when the opposite is the case. If depressants are present and Innovar or ketamine is employed death may result from marked respiratory depression which does not always become apparent immediately after surgery.

I am aware of two such deaths, one from Innovar and one from ketamine and am sufficiently impressed that I urge colleagues to exercise extreme caution in choosing these anesthetic agents for short-term procedures among young patients. Even if the history seems adequate, recovery room personnel should be aware of the potential of secondary as well as primary respiratory depression and patients should not be returned to their rooms prematurely. Innovar and ketamine are excellent drugs, properly used. Regrettably,

the current drug scene makes it imperative that unusual caution be exercised in employing them with potential drug abusing patients.

EDWARD R. BLOOMQUIST, M.D.

Glendale
Chairman, California Interagency
Council on Drug Abuse

Penicillin Reactions

To the Editor: You quote Dr. Eugene S. Hopp (Office Administration of Penicillin, Calif Med 115:60, Sept 1971). He says that he still gives it. I believe that most physicians do give penicillin injections. As Dr. Hopp says, sensitivity to penicillin cannot be predicted. However, allergic reactions to penicillin provoke a large number of malpractice suits. The gravamen in these suits is frequently a contention, contested between the doctor and the patient. The patient says he warned the doctor that he was allergic to penicillin. The doctor says the patient denied having been previously allergic to penicillin.

Although many such lawsuits are filed, I do not know of one where the plaintiff prevailed except on this ground. In giving intramuscular penicillin, it is worthwhile to write, before writing an order (or note) on the chart for intramuscular penicillin, "Patient denies previous allergy to penicillin,"—then on the same line, "Penicillin 600,000 units IM," so that it cannot be said this was added *after* the allergic reaction, and so that when the chart is examined by a plaintiff's attorney and jury, it will be evident that the doctor was thinking along those terms. With this simple precaution, the physician defendant is very likely to prevail.

MURRAY C. ZIMMERMAN, M.D.

Wittier

The Watts Health Miracle

To the Editor: I share with many others still working diligently to see it occur—the increasing feeling of hope brought about by the realization that the long-awaited completion of the Martin Luther King, Jr. General Hospital in Watts, soon to be opened, will truly be the realization of a modern-day miracle on the health horizons.

It has been approximately six years since the violent conflagration in Watts focused attention on the tremendous human suffering of this urban community that continued to be devoid of a major health facility for its many many citizens. The McCoomb Commission Report detailed health needs as one of the major considerations to be given for the community. Subsequent developments resulted in the creation of a Southeast Hospital Authority based on a joint policy agreement between the city and county of Los Angeles which has subsequently served to provide for proper guidance of funding and construction of this facility. As currently designed, this will be a basic unit of 465 acute medical-surgical beds in association with a full range of ancillary laboratory, x-ray and other facilities. An emergency service associated with an outpatient department will provide 24-hour service to the citizens of the area and it is hoped to alleviate one of the major problems of lack of transportation and the severe difficulties encountered by the prior need for patients to travel as much as ten miles for hospital service to the former county hospital (Big General), now known as Los Angeles County-USC Medical Center.

Emphasis on community medicine it is hoped will [accelerate] acceptance [and] understanding of the services available and adequate participation by community physicians and other health providers. The association of the Charles R. Drew Post Graduate Medical School and School of Allied Health & Paramedical-Medical Professionals will lend an academic training component which, it is hoped, will ultimately develop to serve continued education for physicians, nurses and other paramedical professionals.

We began this letter with allusion to the realization of a miracle because a detailed review of the prior reports of the many deficiencies, and the verbal testimony of many of the indigenous citizens who have lived in the area for many years attested the tremendous deprivation of hope and the long feeling that “nothing could happen,” [which] makes completion of this facility a great job and accomplishment to many citizens who feel that this is really a miracle to be realized in their lifetime. The concept is developing around the hospital that this is “our community hospital,” a feeling it is hoped that can be translated into active participation in interpreting an enthusiastic cooperative use of the facility for many years to come.

It seems appropriate with health becoming such a major industry in the nation that the emphasis on this as a constructive element in our society portends a regeneration in the pioneering American spirit. Examine how allocation of national priorities has been made in recent years. Duplication of efforts to provide for human health needs in other communities can be patterned after this effort, both in this nation and abroad, so that man can again believe in miracles to help man and, thereby, assure continuance of our humane survival on this planet.

ELMER A. ANDERSON, M.D.

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Community College Health Services

A Health Care Crisis

E. D. LOVETT, M.D., *Clearlake Oaks*

DURING THE PAST DECADE the community colleges of California have made a dramatic growth in the number of colleges and the enrollment of students. These colleges are making a significant contribution to the educational opportunities within California. Over 300,000 full-time and part-time students are enrolled in college-parallel and terminal-technical-vocational education programs. In addition, the California community colleges provide educational services to more than 400,000 adult students. The importance of their role in education is reinforced by the fact that 86 percent of all current first-year college students are enrolled in the 92 community colleges in the state.

The image of the community college has changed importantly. At one time the two-year college was usually located in the local high school or in a building abandoned by the high school. The educational offerings were often looked upon as the 13th and 14th grades for the financially or academically disadvantaged in the community—a kind of second-rate institution of higher education. In general the community college of today is located on its own campus, has an academically respectable faculty, and provides educational programs of high quality. More than 30 percent of the community college stu-

dents in California eventually transfer to a four-year institution and nearly 80 percent of these students obtain a four-year degree. From this it may be seen that more than 100,000 community college students enter four-year colleges and universities each year and 80,000 of them eventually receive a degree. Briefly, the community college is a two-year post-high school institution offering college-parallel, terminal-technical-vocational, and adult education instruction directed to the community's needs. It is an open-door, low cost, locally controlled institution with a student body composed of a cross-section of the population of the community with a broad spectrum of interests, aptitudes, backgrounds, aims, achievements and cultural mores. Many of the students need remedial assistance for a variety of needs before either job preparation or further advancement on college work. The community college cannot be compared with the institution taking top students, with a high selectivity, high tuition charges, residential programs, and a liberal arts emphasis.

A common attitude inherited from the past that community college students are all living at home and are under the protection of the home and the family physician is not altogether true. Many students are found to declare their independence by living outside the home. Some students are reluctant to consult the family physician, for any of the following reasons:

- A significant number do not have a family physician.

Part of the Symposium on School Health: Look to the '70's, at the Special Conference, Congress on Health of the School-Age Child, presented by the CMA Committee on School and College Health, at the 100th Annual Session of the California Medical Association, Anaheim, March 13 to 17, 1971.

Reprint requests to: P.O. Box 506, Clearlake Oaks, Ca. 95423 (Dr. E.D. Lovett).

- Many do not wish to consult the family physician because they have no confidence in the confidentiality of the visit.

- The high cost of private health care.

- Surveys of a limited number of two-year college health programs revealed as few as 32 percent of students had coverage under any kind of comprehensive family health insurance.

- The "independence" (student's term) of the private physician may cause the student considerable loss of time. When the student called for an appointment, he is often told to come in and wait and he would be "squeezed" in, resulting in several hours of lost time.

- Many physicians do not wish to be "bothered" with student referrals.

The two-year colleges of California are showing a growing interest in campus health programs. Trebbe¹ made a study of 89 two-year colleges in California (88 percent reporting) which revealed that 52 (67 percent) of the colleges had a student health center. Fifty-six (72 percent) employed a school nurse for an average of 34 hours a week. Dr. William Wanamaker [a participant in the Symposium on School Health] reported a study of 18 community colleges in California which found only three physicians as regular staff members of the health program. Most of the health centers are staffed solely with nurses. Overall, these nurses are doing a commendable job. Because it is unlikely that the community colleges will be able to justify a complete staff of physicians, the nurse must depend on the cooperation of the local medical, hospital and health resources of the community.

My principal aim in this presentation is to urge the physicians of California to become involved with the health programs of their community colleges. This means more than "doing your duty" by appointing a school and college health committee in your county medical society and in CMA, important as these groups have been. One of the most personally satisfying things you can do is to invest some time on the campus and in the health center, becoming involved with and understanding the current crop of college students. Beneath that long stringy hair, the beards and the sloppy clothes are real, live human beings with high ideals and the energy to pursue them. They are not your enemy unless you make them so. Don't knock them until you have some understanding of them.

The second pay-off for you is the opportunity to engage in an informal exchange of information concerning the here-and-now health problems of students. I say *exchange* because they will teach you as much as you will teach them—that is, if you have the capability of engaging in a two-way communication. Two-way communication in this situation means an interaction between two people through the sending and receiving of information. It is a process whereby the sender attempts to influence the recipient of the message, and the recipient has an equal opportunity to influence the sender (I will let you try to make me a Democrat if you will give me an equal chance to make you a Republican). These students may challenge or threaten some of your firmly held views and they will send you into retreat if you take an automatic stance on health matters: "I am the doctor and I know best." I invite you to become involved with your community college. I suggest you visit the campus and its health service regularly and polish the somewhat tarnished image of the medical profession and, by your actions, contradict the idea that physicians in general are money-grabbing, inhuman and remote. These students are not only going to be your patients; they are also going to influence the type and quality of medical care of the future. You have a rare opportunity to participate in health education of the most useful kind, to the benefit of the students and the medical profession.

Let me briefly outline the role of the community college health service. It is the generally held opinion that the community college health program should provide the following services:

- First aid and emergency care on the campus.
- A referral resource for illness and injury.
- Preventive medicine by making provision for immunizations, skin tests, chest x-ray studies and other preventive measures.

- A resource for health counseling and health education.

The above services are essential and should have a high priority, but other services are just as important. They are:

- *The admission health inventory.* The health status of the student should be known at the time of admission to the college. At a minimum, the college health service should have enough information to classify the student's health capability as to physical education activity, special

privileges (parking, elevator key, and the like), the eligibility for participation in sports, and special health problems (such as epilepsy or diabetes) which may influence the student's educational progress.

- *A campus health information center.* A central station to collect and analyze campus health information and report its significance to the administration, advise faculty concerning student health problems, and advise students and faculty requesting health information.

- *An environmental health and safety office.* Inspection and supervision of health practices in the food and housing activities, maintain an on-campus accident log for the elimination of actual and potential hazards in the laboratories and shops, and recommend on-campus safety procedures (eye baths, showers, safety glasses, safety lighting).

- *Mental health service.* Surveys of the mental health of various populations reveal from 30 percent to 40 percent are handicapped to some extent by psycho-physiological, psychoneurotic, or other disabling emotional behavior. Ten percent of all college and university students seek counseling for personal emotional problems when this service is available. The health service can make a solid contribution by involvement with instructors and counselors in helping students learn to handle personal problems, to counsel students with health problems relating to academic performance, to provide support during stressful and crisis situations; and a referral resource for short and long term psychotherapy.

- *Outpatient clinic service.* For the protection of the student and the college, the campus health program should be under the supervision of a physician. The trend is toward the utilization of part-time physician services.

- *Sex education.* You cannot make students live up to moral standards by law or regulations. The cultural change in attitude toward discussing sexual attitudes and behavior should be recognized. Sex education and family planning information should be available to college students. A venereal disease education and control program is an essential component of a campus health program. The success of the program depends on strict confidentiality of the student's medical record and close liaison with the student's physician and the local health department.

- *Drug abuse center.* Drug abuse among students is a horrendous problem. There is no question that continued drug abuse has a destructive influence on the user. I am convinced that we do not know the best solution to this problem, simply because we don't know how to prevent drug abuse and, once the individual is taking drugs, how he should be treated. The current approach to the problem can be divided into: (1) drug education, (2) treatment, and (3) rehabilitation. Treatment and rehabilitation should be left to the recognized community resources. The health service can be effective in drug education. The more successful programs have a number of guidelines:

- (a) A passive, accepting, and "no-heat" policy.

- (b) A sincere attempt to understand the drug abuse culture and the feeling behind it.

- (c) An indirect educational approach. Formal lectures and forums, in my experience, generally have little lasting influence. Informal discussion groups and adjustment seminars, held outside the health center or off campus and led by former users, have been reasonably effective. The physician is often invited as a resource person, though unfortunately, most physicians have little knowledge applicable of the present drug problem.

- (d) Confrontation or moralistic preaching either breaks all future contact or leads to arguments and debates.

- (e) Laws, rules or regulations are *not* effective tools in curbing drug abuse.

- (f) Expelling the student solves the college's problem, but does nothing to bring the student back into society and give him a chance to achieve a degree of successful living.

- (g) A 24-hour panic or crisis answering service on the campus or in the community has been beneficial service.

The crisis in the total health status of the community college student is due to:

- The rapid expansion of the number of colleges, the enlarging enrollments, and the high quality of educational offerings of the community colleges of California.

- The great need and opportunity to provide here-and-now health education and fundamental information whereby the student may make appropriate decisions concerning his own health, and contribute a knowledgeable voice in the pro-

vision of community health care including the ecology, the care of the underprivileged, and the most beneficial health delivery systems.

- The necessity of providing a health service program to meet the physical and emotional health needs of the students through the cooperative efforts of on-campus and community health resources.

The crisis can be met in part by the aggressive activities of the school and college health committees of organized medicine. The greatest impact can be provided by the personal involvement of the individual physicians of California in their local community colleges.

1. Trebbe ES: Current Practices of Student Personnel Services in the Community College of California. Campbell, West Valley Junior College. Unpublished.

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101st

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All-Day Conference on Venereal Disease

Allergy for the Non-Allergist

Criteria for Coronary Bypass Surgery

*Newer Aspects of Dermatologic Problems
of the Foot*

*All-Day Conference on Physician
Responsibility and Drug Abuse*

Pelvic Cancer in the Liberated Sex

Diabetes Mellitus

Symposium on Surgery of the Colon

Current Status of Surgery of the Thyroid

Chest Diseases

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Medical Education Today—for What?

Acute Trauma

Bell's Palsy—How Should We Treat It?

*Complications Following the Treatment
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Excellence Need Not Cost More

Relating a Free Clinic's Services to the Patient's Convenience and Feelings

LEONARD M. PARKER, M.D., *Hayward*

HIGHLAND GENERAL HOSPITAL is the acute care public hospital facility for Alameda County, which lies on the east shore of San Francisco Bay. The hospital was founded in 1926 and in February, 1970, completed and occupied a new facility containing 313 beds. Adjacent to the hospital is a Mental Health unit consisting of 73 beds and extensive outpatient services. Highland is located in Oakland and, as with most public hospitals, serves a minority and indigent population. Highland Hospital is approved for and has filled its 42 intern positions for many years. There are also 91 residents enrolled in 13 specialties. Highland, like most county public hospitals in the past, was medically run by house staff with the loyal but sporadic services of a large visiting staff. During the past five years many full-time medical staff have been added so that all major services have at least one, and in some instances two, full-time physicians. This has afforded opportunity for a careful analysis of the services offered by the hospital and of the means required to correct the shortcomings of such an institution.

The Problem

The Obstetric and Gynecologic service of Highland Hospital (like most of the specialty

clinics) had been established along the traditional lines with essentially two mass clinics—obstetrics on one day and gynecology on another. Three smaller sub-specialty clinics were conducted; namely, Abortion, Gynecologic-Cancer and Endocrinology. No effective appointment system existed and all patients were told to report at 7:30 a.m. The clinic began at 8:30 a.m. and ran until noon for obstetrics and until 4:00 p.m. for gynecology. Nine examining rooms were used and were staffed by the six OB-GYN residents and three interns. Pre-registration for billing was conducted for all clinic patients on the first floor and the OB-GYN patients were then weeded out and directed to the third floor where they would have to register again to obtain a sequential number. Inasmuch as some patients could not be seen until noon, the waiting time could be up to three to five hours. Save for what socializing could be done in the hallways, the waiting period was of no benefit.irate patients, short-tempered clerks and howling children were the ordinary. From one obstetric appointment to the next, the patient's only recourse to information or advice was handled by the switchboard operator who referred the patient to an already overloaded emergency service. No means of relating with "my doctor" or even "the obstetric clinic" was available because this clinic space was used on the other three and a half days by such other specialties as Dermatology, Allergy

From the Department of Obstetrics and Gynecology, Highland General Hospital, Oakland.

Submitted May 14, 1971.

Reprint requests to: 2457 Grove Way, Hayward, Ca. 94546 (Dr. L. M. Parker).

and Urology. An obstetric patient with constipation would remain in this state until her next obstetric appointment, or else would go to the Emergency Department to vie for attention with approximately 150 daily emergency patients including those with stab and gunshot wounds and those injured in highway accidents.

The Beginning of the End

The first change in the system, undertaken in the Fall of 1969, was to eliminate the pre-registration lines and to stagger the times of appointments. Information for billing and for other needs was obtained all at one time, when the patient arrived. The patient then was directed to a large pleasant waiting room from which she was summoned by intercom to the examining room. During the patient's time in the waiting room, a pre-announced teaching program was held. It included the showing of films and discussions by nurses, physicians, nutritionists, social workers, and public health nurses, aimed at giving patients supplementation to their original prenatal teaching interviews. Even patients who did not become involved in the discussions were nonetheless exposed to it. This program also showed the human side of the hospital as distinguished from the remoteness that caused patients to say "Highland did this" or "those Highland doctors" or "those Highland nurses." Nonetheless, the clinic continued to run in the same fashion—nine open cubicles with only one layer of cotton drape separating one patient's problems from another patient's initial pelvic examination. Although for shorter periods, absenteeism of doctors (residents) from the clinics continued because of responsibilities they also had for deliveries, emergency surgical operations and coverage of the emergency room consultative service. But one thing was apparent: We had the personnel, the skills, the experience and the patients. All we had to eliminate was the complacency.

The End of the Beginning

During the summer of 1970, a self-contained unit adjacent to the clinic area was accidentally discovered by the OB-GYN Department. This area previously contained clerk-typists who were each assigned a room equipped with a sink, bright

lighting and windows. Besides the six rooms, the unit also contained a reception area, a toilet, a laboratory and a work room. Soon after it was discovered, the unit was painted and redecorated and converted into four examining rooms, one consultation room and a waiting room. Daily appointments were made at 15-minutes for two doctors. The doctors assigned to the clinic were a resident and an intern. The resident rotation was of three months' duration, the intern rotation was every three weeks. During the rotation, these physicians had no inpatient or emergency room responsibilities. They did, however, take night calls in rotation. In addition, the area formerly used was abandoned by the OB-GYN Department and the mass clinics that had been conducted there were discontinued. The five remaining residents were then given one afternoon a week to see patients whom they personally scheduled. In general, each of these residents sees eight to twelve patients per weekly session for postoperative observation or for infertility, endocrinologic or other problems. Patients began to relate to a specific physician and continuity of care following hospitalization was more assured. Gynecologic-Cancer and Abortion clinics are still held separately from the "office."

The clinic operates from 8:00 a.m. to 4:00 p.m. weekdays, and patients are given a choice of day and hour. Appointments are made immediately either after the visit or by telephone in the decentralized clinic rather than in the central appointment area. Having two physicians available in the clinic eight hours a day plus a permanent nursing staff has enabled patients to call in and have minor problems handled by telephone. The personnel are able to handle or make a special appointment for problems which cannot wait until the next scheduled appointment. Emergency cases are still handled through the Emergency Department in the usual manner and OB-GYN consultations are available by a physician other than one assigned to the clinic.

Our patient teaching program has been altered in that there are now two prenatal teaching experiences conducted by a full-time OB-GYN nurse coordinator. She does the initial intake of the patient—history, laboratory work and the like—and conducts a class for the pregnant patients. She also conducts La Maze classes in the evening (the first utilization of this clinic building

during other than the usual "county hours"). In the waiting room informational films are shown on a cassette film-viewer.

Nursing staff in addition to the OB-GYN nurse coordinator consists of a full-time staff nurse, one licensed vocational nurse, one nurse's aide, one clerk and one half-time registered nurse. In the former set-up, we required 156 hours of fragmented, rotating nursing and aide time. Currently, we use 140 hours of full-time personnel who can establish a continuing relationship with patients. Under the old system, we required the use of four clerks, one each for pre-registration, processing-in, processing-out, and appointments. These functions have been assumed by one full-time clerk who has performed with a courtesy and efficiency not always apparent in the past. All personnel involved initially volunteered for these jobs, and there have been no requests for transfers out. On the contrary, we have had many requests for transfers into the unit.

Results

The waiting time for patients has been reduced to approximately 10 to 15 minutes. We still occasionally find that a chart has been misplaced, but this is not frequent. Patients experienced in the "old system" comment favorably on the changes. Some patient education was required to assure the patients that their appointed time was indeed reserved for them. This helped to decrease the "no shows" and tardiness. The house staff all were pleased with the change. They are receiving a realistic look at office practices and procedures never before offered as part of their training. Clinic teaching is maintained by hav-

ing the full-time staff come to the clinic frequently to handle problems as they arise. The chief residents are in and out of the clinic all day, helping in consultations and in the training aspects of the program.

The clinic staff has begun to receive amenities previously unknown—cakes, thank-you notes, pictures of newborn infants, cookies and, most gratifying of all, "smiles." With cessation of the mass clinics which tied up the house staff for approximately two full days each week, the remaining staff now has more time for study. Our Medical Records Department reports that chart deficiencies have also decreased with this newfound time for the house staff.

Although we feel we have made great strides since the initiation of the program, only a part of the problem has been tackled. Our "office" needs to be run in the evening and on weekends; baby-sitting services should be made available, transportation to and from the clinic should be more accessible and attitudes throughout the entire institution must be changed. Until all clinics and services in the institution have adapted themselves to the needs and comforts of their patients, we shall continue to operate in a vacuum separate and alienated from the indigent community we serve. We must accept the fact that only with intelligent, concerned and non-bureaucratic leadership can we offer dignified and responsive services. This can be done at less cost and with greater efficiency than in the past, which was represented by less than adequate, fragmented, and crisis-oriented care. The problem is too apparent and real to require further time-consuming and expensive studies.

Excellence need not cost more.

NO FOOD BY MOUTH FOR TACHYPNEIC INFANTS

Any infant that is severely short of breath is likely to aspirate oral feedings. . . . Because of the frequency of aspiration in tachypneic infants, I think (particularly when it is an acute process) that oral feedings ought to be withheld and the infant should either be maintained by intravenous feedings or have a feeding tube put down. We repeatedly see tragedies when feedings are given orally in infants who are in fairly profound degrees of respiratory distress. I think this is true regardless of the cause of the respiratory distress.

—JAMES B. SNOW, JR., M.D., Oklahoma City
Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 3, No. 7,
in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057

PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H., Director, State Department of Public Health

Conserving California's Water

CALIFORNIA IS FULLY committed to the proposition that water is a commodity which should not be used once and then discarded. As expressed in the Water Code, "It is the intention of the Legislature that the State undertake all possible steps to encourage development of water reclamation facilities so that reclaimed water may be made available to help meet the growing water requirements of the state."

The encouragement of waste-water reclamation and reuse is not a new philosophy in the State. Since the turn of the century, California has used sewage effluent for irrigating fodder and other non-food crops such as cotton, alfalfa and seed corn. The March 1910 *Monthly Bulletin* of the State Board of Health recommended that "in California, where water is so valuable for irrigation, the utilization of sewage for broad irrigation should be carefully considered."

In the last two decades, the trend has been toward uses of reclaimed water even where there is more public exposure—for example, the irrigation of golf courses, parks and freeway landscape and the filling of recreational and ornamental lakes. In 1955 perhaps a half-dozen golf courses were irrigated with reclaimed water and at that time the practice was looked upon as undesirable but necessary. Now 45 systems produce water for public areas—51,000 acre-feet of water capable of irrigating about 15,000 acres—with good public acceptance.

In the popularization of wastewater reclamation there is a tendency to minimize the point that the basic material to be reclaimed (sewage) is a hazardous substance which must receive adequate and reliable treatment. The switch

from the term "sewage effluent reuse" to "water reclamation" is probably a manifestation of this tendency. Health authorities are constantly aware of the source of reclaimed water, and the principal efforts of the Department of Public Health in this field have been directed at two critical aspects of reclamation: assuring both *adequate* and *reliable* treatment of reclaimed water.

In 1938, the State Board of Public Health adopted regulations on the use of sewage effluent for crop irrigation. The regulations required a settled sewage for irrigation of fodder, fiber and seed crops, and set very strict limits on the bacteriological quality of sewage effluent which could be used for food crops.

These regulations served very well through the years. Crop irrigation was essentially limited to non-food crops and was carried out without excessive odor or other nuisances. With the advent of the new uses of reclaimed water, additional quality requirements were needed; however the statutory authority under which the 1938 regulations were adopted had been repealed in 1949. In a hearing before the Assembly Committee on Water in 1965, the Department stressed the need for an "unequivocal assignment of responsibility and authority to cope adequately with the wide range of new exposures to the public to reclaimed sewage which is just now coming into view." The committee responded with recommended legislation which became a part of the Porter-Cologne Water Quality Control Act of 1967 and authorized the Department to establish quality standards for various uses of reclaimed water. In 1968, the State Board of Public Health adopted standards of quality for reclaimed water used for such purposes as park irrigation, filling lakes for boating and fishing, and other uses which are coming on the scene.

In addition to meeting a quality standard which will assure that the reclaimed water is safe for the intended use, there is the second vital element which enters into the safe produc-

tion of reclaimed water, namely, there must be assured reliability of the operation. Sewage treatment plants have had a very poor record in this regard, and features which provide reliability have not been sufficiently emphasized in the past. Elements such as duplicate units, remote-sounding alarms, emergency power supply, and stand-by disinfection equipment are an added expense and often have not been provided. Consequently, a revision was made in the Porter-Cologne Act to enable the Department of Public Health to establish the "means for assurance of reliability" in reclamation operations. The Department undertook two intensive surveys of reclamation systems in 1969 and 1970 to gather information on the present provisions for reliability in reclamation plants and to determine just what is needed to assure the

ability of the operation to produce a safe product, reliably and consistently. It is now developing reliability criteria which are undergoing Departmental review by a board having a wide range of experience and expertise.

Water reclamation is a reality in California where 132 reclamation operations now reclaim 46 billion gallons of water each year. It is an essential part of the contemporary movement to conserve natural resources and preserve environmental quality. With provisions for maintaining the reliability of reclamation systems and the production of water of suitable quality for the intended use, as well as reasonable precautions to prevent unnecessary exposure of the public to reclaimed water, it is possible to carry out a reclamation program which safeguards the health of the public.

A PROGNOSTIC INDEX IN MYOCARDIAL INFARCTION

Traditional clinical techniques of evaluating patients with acute myocardial infarction and categorization according to clinical signs of circulatory failure present at admission (a system proposed by Killip and colleagues) are immensely useful in predicting groups with a low, intermediate, and extremely high mortality. One of the major questions we have had though is whether measurement of hemodynamic variables would improve this prediction and if so, which variables would be the most helpful.

We are presently evaluating the prognostic index based upon hemodynamic data obtained at the time of admission. The index was designed to predict hospital survival or death. The variables in the index include the arteriovenous oxygen difference, stroke index, right atrial pressure, and systolic arterial pressure. . . . The first variable, the ratio of the arteriovenous oxygen difference to stroke index, is by far the most important in the equation.

Our preliminary data indicate that this index is successful in predicting survival with better than 95 percent accuracy and in predicting hospital death with better than 80 percent accuracy. . . . The measurement of certain hemodynamic variables at the time of admission to a coronary care unit provides information that is not apparent from the physical examination in about one out of every five patients. . . .

We believe that the determination of the arteriovenous oxygen difference coupled with the clinical classification proposed by Dr. Killip provides the best available index of prognosis for hospital survival or death.

—ANDREW G. WALLACE, M.D., Durham, N.C.
Extracted from *Audio-Digest Internal Medicine*, Vol. 18, No. 4, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057

Proposed CMA Constitutional Amendments

FOR ACTION IN 1972

Two Constitutional amendments were introduced in the 1971 House of Delegates. Under the terms of the Constitution, these amendments must lie on the table until the next regular meeting of the House of Delegates.

These proposed amendments are shown here for the information of the membership. In addition, the proposed Constitutional amendments are required to be printed in two issues of CALIFORNIA MEDICINE before it comes before the House of Delegates for action.

VOLUNTARY MEMBERSHIP IN CMA AND AMA BY A MEMBER OF A COMPONENT COUNTY MEDICAL ASSOCIATION ARTICLE I, SECTION 3

Constitutional Amendment 1-71 Committee G
Introduced by: Allan K. Briney, M.D.

WHEREAS, the present bylaws of the CMA make membership in the CMA and AMA compulsory to all members of a component county medical society; and

WHEREAS, we, as a profession, vigorously defend the principle of "freedom of choice" in health care, yet deny individual members of county medical societies the freedom of deciding whether or not they wish to belong to the CMA or AMA; and

WHEREAS, each physician is quite capable of deciding whether there are sufficient advantages or insufficient advantages to maintaining membership in all three organizations; and

WHEREAS, mandatory membership in one organization (CMA and AMA) in order to maintain membership in another (local medical society) significantly interferes with the privilege of setting priorities as to organizational commitments, such as belonging to specialty societies; and

WHEREAS, many individual "grass roots" county

medical society members feel the CMA Council and officers, and the AMA Board, officers and delegates do not generally reflect their attitudes and concerns; and

WHEREAS, in many states a local county medical association member may decide for himself whether he also wishes to maintain membership in the state and national medical associations, e.g., New York and Massachusetts; and

WHEREAS, professional liability insurance carriers have no requirements about CMA or AMA membership for coverage of a county medical society member; and

WHEREAS, insurance brokers are delighted to sell insurance of all kinds under a variety of different organizational arrangements, making it no significant advantage to belong to the CMA or AMA for insurance enticements; and

WHEREAS, in a free and democratic society it would seem reasonable and consistent that membership in all medical societies should be voluntary, with each society attracting members on its own merits; and

WHEREAS, when a local county medical association collects dues for a state and national medical association, the individual dues-payer tends to lump all these dues together as "county medical society dues," feeling he may not be "getting his money's worth"; and

WHEREAS, recent events in higher levels in AMA politics indicate that a group which does not represent the view of the majority of practicing physicians has assumed control over AMA policy, with the result that physicians in private practice (the mainstream of American medicine) are being asked to accept ideas such as compulsory or "universal" national health insurance that the AMA opposed as recently as 1965, and with the result that an effort to create a Council on Private

Practice was voted down by steamroller tactics in the House of Delegates, and with AMA failure to oppose interference with the practice of medicine by the Department of H.E.W.; and

WHEREAS, there is widespread feeling among local county medical association members that the CMA and AMA have long ago lost their "grass roots" contact and cannot speak authoritatively for the medical profession; now, therefore, be it

Resolved: That Article I, Section 3, be amended as follows:

This Association is an organization composed of the component societies and their members who are members of this Association, the House of Delegates, the Council, the Scientific Board, the Scientific Assembly, Bureaus, Commissions and Standing Committees.

ACTION: *Tabled for one year. To be acted upon at the 1972 meeting of the House of Delegates.*

(TERMS OF OFFICE—COUNCILORS)

ARTICLE III, PART B, SECTION 12

Constitutional Amendment 2-71 Committee G

Introduced by: David B. Horner, M.D.

WHEREAS, the Councilors of the California Medical Association are elected to serve a term of three years; and

WHEREAS, there is no restriction on the number of terms that a Councilor can be elected and serve; now, therefore, be it

Resolved: That Article III, Part B, Section 12, of the Constitution of the California Medical Association be amended as follows: "Section 12.—Councilors: Terms of Office. Councilors shall serve for a term of three (3) years; one-third to be elected in each year. A Councilor shall not serve more than three (3) consecutive terms of office."

ACTION: *Tabled for one year. To be acted upon at the 1972 meeting of the House of Delegates.*

WHEN TO OPERATE IN GI HEMORRHAGE

The therapeutic approach I favor in patients with massive upper gastrointestinal hemorrhage utilizes medical therapy except when one can't stabilize the patient with 1,500 to 2,000 ml of blood in the first 24 hours. I operate when there is recurrent bleeding in patients on adequate medical therapy, especially if more than 1,000 to 1,500 ml of blood is needed by the third day to maintain stability. (I incline more toward the 1,000 ml than the 1,500 ml figure.)

This approach can sometimes prevent unnecessary operation in younger patients with an acute rather than a chronic ulceration. It focuses attention on the rate of bleeding, which is fundamental to the circulatory stability of the individual; and it permits some individuals to stop bleeding and (if indicated) be operated on at a later date under elective conditions with a much lower mortality. Also if the bleeding is due to an avoidable cause like aspirin administration, the cause can be removed with less likelihood of further difficulty.

However, certain factors such as initial shock, the older age group (by that I mean the physiologic rather than the chronologic age), and the presence of concurrent disease should make one a good deal less eager to adopt a conservative stance; one should recognize the steadily increasing mortality rate with long delay in this group and be more willing to operate earlier in the game.

—DOUGLAS A. FARMER, M.D., New Haven
Extracted from *Audio-Digest, Surgery*, Vol. 17, No. 24, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057

Information

Extracorporeal Circulation

Part II

ROBERT S. LITWAK, M.D.

*Material Supplied by the American
Heart Association*

THE RISK OF COMPLICATION associated with cardiopulmonary bypass is remarkably low, perhaps one percent for perfusions lasting three hours or less. Factors etiologic to risk are related to (1) the equipment, (2) the perfusate and (3) technical execution of the procedure.

Existing equipment places blood in contact with varyingly antagonistic foreign surfaces and subjects it to unphysiologic flow conditions due to narrowed cannula and tubing sizes, angulation and foaming. These combine to cause measurable destruction of all formed elements and alteration of blood proteins. Excessive postoperative bleeding may be observed and is generally associated with or is the result of thrombocytopenia and increased fibrinolytic activity. Significant anemia may be noted five to ten days after operation due to delayed red cell destruction. Although open heart operations can be performed in specific cases without need of donor blood, this has not yet become routinely practical in all cases. Serum hepatitis is perhaps the most common complication of extracorporeal circulation and is roughly proportional to the amount of blood (and therefore the number of donors) required. A postperfusion febrile syn-

drome with a hematologic pattern similar to that of infectious mononucleosis, probably caused by cytomegalovirus, has also been shown to be associated with infusion of large quantities of donor blood.

Certain complications are related to technical details of operative management. Air embolus results from failure to completely fill the pulmonary veins and the left heart with blood before discontinuance of perfusion. Particulate emboli consisting of loose remnants of intracardiac thrombi or calcific fragments may be lethal, particularly if they lodge in the coronary or cerebral arterics. Arterial cannulae positioned in atherosclerotic femoral or iliac arteries may occasionally induce retrograde dissections of these vessels. When these arteries are extensively diseased, cannulation of the ascending arch of the aorta is advisable.

The postperfusion state tends to be accompanied by measurable but tolerable alterations in organ function. Postoperative low cardiac output is often of hypovolemic or brady-arrhythmic origin. Maintenance of proper intravascular volume is best achieved by using left or right atrial pressure measurements as guides to blood or colloid administration. Arrhythmias, particularly if associated with slow heart rates (50 to 70 per minute), are often effectively managed by rate augmentation employing atrial or ventricular pacing with wires implanted at operation. Discontinuance of digitalis preparations several days before operation and avoidance of postperfusion hypokalemia will further reduce the incidence of postoperative arrhythmic problems.

Some degree of ventilatory and respiratory dysfunction is commonly observed, especially in patients who have been in preoperative chronic left heart failure or when perfusion has been protracted. Reduced diffusion of oxygen from the alveoli into the pulmonary capillaries results from a combination of factors. Elevated arterial carbon dioxide tension in the early postoperative period is commonly the result of right to left shunting through atelectatic areas of the lung which are perfused but unventilated. Tracheal intubation and mechanical ventilation has been effective in management of these problems.

In the absence of blood incompatibility, postoperative renal failure consequent to perfusion *per se* is rare. It is probable that the hyper-

Part II of a two-part article. Part I appeared in the October issue.

Dr. Litwak is from the Division of Cardiothoracic Surgery, Department of Surgery, Mount Sinai School of Medicine, New York City.

osmolar hemodilute perfusate used in most centers exerts a salutary effect in minimizing the incidence of this complication. When renal failure occurs (particularly acute tubular necrosis) it is generally observed in debilitated patients in cardiac failure who have nitrogen retention before operation and a pattern of low cardiac output in the postoperative period. Precise intraoperative management and postoperative support and maintenance of cardiac output should reduce this complication to a minimum.

Emotional disturbances ranging from confusion, visual and auditory hallucinations to frank psychosis may develop in certain patients following open heart operations. These are almost exclusively observed in adults and are believed to be caused by a combination of factors, including perfusion trauma, preoperative and postoperative apprehension, and lack of appropriate sleep patterns due to continuing activity in the intensive care unit. Constant reassurance and judicious sedation are required. Fortunately, the

behavioral patterns tend to return to normal within two weeks of operation.

It is almost certain that further improvements in design of extracorporeal circulatory and gas exchange systems will expand permissible periods of use to days or weeks, thereby making prolonged cardiac and respiratory assistance a practical reality. Ideally, such systems will not require donor priming blood or systemic heparinization of the patient. Thus, low prime disposable pump-lung units with no direct gas-blood interface made of thromboresistant materials are required. There is urgent need for a non-toxic, non-antigenic plasma-like fluid capable of oxygen transport which can be used to prime extracorporeal circuits and replace blood lost during and after intracardiac and prolonged support procedures. Finally, the importance of pulsatile blood flow requires further study since there is accumulating evidence that such a flow pattern enhances organ function under perfusion conditions.

WHEN TO OPERATE IN CHRONIC GLAUCOMA

Years ago in ophthalmology, we felt that chronic simple glaucoma should have operative treatment and we did the surgical operation almost as promptly as in the narrow-angle glaucoma. That quite obviously is wrong and this represents one of the great advances to come from knowledge obtained by gonioscopy. However I feel rather strongly that at the moment we are leaning over backwards and not operating on patients who deserve to be operated upon. . . .

I am not urging universal surgical operation for chronic simple glaucoma. We are saving numerous eyes by not operating. . . . I urge and I teach our residents to use maximum medical therapy before they resort to surgical operation. . . . But I do feel that when you are convinced an eye is going to go down hill, the patient should be operated upon. Filtering operations are not so devastating that we should permit blindness or near-blindness to occur. I've seen a number of patients in consultation whose histories over a period of three to five years clearly showed an eye going down hill to a small field. This development could have been prevented if surgery had been done some years before.

So I put in this plea for what it's worth. I urge conservatism, but there comes a time when conservatism is no longer justified and then it's more conservative to be just a little bit radical and intervene.

—HAROLD G. SCHEIE, M.D., Philadelphia
Extracted from *Audio-Digest Ophthalmology*, Vol. 9, No. 1, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057

In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

ALLEN, WARREN BARRETT, Oakland. Died September 11, 1971 in Cortaro, Arizona of congestive heart failure, aged 84. Graduate of University of California Medical School, Berkeley-San Francisco, 1913. Licensed in California in 1913. Doctor Allen was a retired member of the Alameda-Contra Costa Medical Association, and the California Medical Association, and an associate member of the American Medical Association.

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ANDONIAN, ANDON ARMAND, Los Angeles. Died September 15, 1971 in Pasadena, aged 48. Graduate of University of Tehran College of Medicine, Tehran, 1948. Licensed in California in 1954. Doctor Andonian was a member of the Los Angeles County Medical Association.

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BISEL, JERALD NATHANIEL, Pittsburg. Died September 28, 1971 in Pittsburg of cerebral hemorrhage, aged 39. Graduate of Loma Linda University School of Medicine, Loma Linda-Los Angeles, 1965. Licensed in California in 1966. Doctor Bisel was a member of the Alameda-Contra Costa Medical Association.

**

BLOSSOM, ROBERT, Ventura. Died August 24, 1971 in Ventura of multiple sclerosis, aged 48. Graduate of St. Louis University School of Medicine, 1948. Licensed in California in 1948. Doctor Blossom was a retired member of the Ventura County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

**

BRADBURY, WILLIAM C., Los Angeles. Died September 15, 1971 in Loma Linda of cerebral infarction, aged 64. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1935. Licensed in California 1935. Doctor Bradbury was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

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CANTU, JAIME TEOFILO, Los Angeles. Died September 22, 1971 in Lakeview Terrace of heart disease, aged 48. Graduate of Escuela de Medicina de Nuevo León,

Monterrey, Mexico, 1951. Licensed in California in 1955. Doctor Cantu was a member of the Los Angeles County Medical Association.

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CORNELIUS, LAWRENCE R., San Diego. Was killed September 4, 1971 near Juneau, Alaska in an airplane crash, aged 49. Graduate of University of Cincinnati College of Medicine, 1952. Licensed in California in 1954. Doctor Cornelius was a member of the San Diego County Medical Society.

**

FRANKLIN, CHARLES THOMAS, La Mesa. Died August 27, 1971 in London of cancer, aged 44. Graduate of Georgetown University School of Medicine, Washington, D.C., 1949. Licensed in California in 1950. Doctor Franklin was a member of the San Diego County Medical Society.

**

GOURLEY, INA, Livermore. Died September 21, 1971 in Livermore, aged 78. Graduate of State University of Iowa College of Medicine, Iowa City, 1922. Licensed in California in 1929. Doctor Gourley was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

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HILL, JACK C., Pasadena. Died September 11, 1971 in San Jose, aged 87. Graduate of College of Physicians & Surgeons, Medical Dept., University of Southern California, 1918. Licensed in California in 1918. Doctor Hill was a retired member of the San Bernardino County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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HOWARD, WAYNE COX, Los Angeles. Died September 22, 1971 in Los Angeles of myocardial infarction, aged 58. Graduate of University of Illinois College of Medicine, Chicago, 1939. Licensed in California in 1945. Doctor Howard was a member of the Los Angeles County Medical Association.

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KNORP, WILLIAM FREDERICK, San Mateo. Died September 24, 1971 in San Mateo, aged 70. Graduate of University of California Medical School, Berkeley-San Francisco, 1928. Licensed in California in 1928. Doctor Knorp was a retired member of the San Mateo County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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KOLTS, ROBERT F., Glendale. Died August, 1971, aged 75. Graduate of College of Osteopathic Physicians & Surgeons, Los Angeles, 1925. Licensed in California in 1925. M.D. degree from California College of Medicine, 1962. Doctor Kolts was a member of the Forty First Medical Society.

LITTLEFIELD, DON CLAUDE, Ukiah. Died July 30, 1971 in Mariposa, Alaska, of heart disease, aged 61. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1938. Licensed in California in 1938. M.D. degree from California College of Medicine, 1962. Doctor Littlefield was an associate member of the Mendocino-Lake County Medical Society.

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MADDEN, DONALD JOSEPH, Santa Monica. Died August 13, 1971 in Mar Vista of heart disease, aged 45. Graduate of The Creighton University School of Medicine, Omaha, 1948. Licensed in California in 1950. Doctor Madden was a member of the Los Angeles County Medical Association.

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MAURER, ROBERT D., Tracy. Died August 28, 1971 in Tracy, aged 61. Graduate of Western Reserve University School of Medicine, Cleveland, 1936. Licensed in California in 1940. Doctor Maurer was an associate member of the San Joaquin County Medical Society.

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MEYER, HANS A., San Francisco. Died July 30, 1971, aged 80. Graduate of Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, 1916. Licensed in California in 1937. Doctor Meyer was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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NEVIUS, JOHN WILSON, Arcadia. Died August 31, 1971 in Arcadia of acute myocardial infarction, aged 92. Graduate of University of California Medical School, Berkeley-San Francisco, 1911. Licensed in California in 1911. Doctor Nevius was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

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NEWMAN, HOWARD, La Mirada. Died September 7, 1971 in La Mirada of fulminating viral hepatitis, aged 30. Graduate of University of Tennessee College of Medicine, Memphis, 1966. Licensed in California in 1967. Doctor Newman was a member of the Los Angeles County Medical Association.

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PETERSON, JOSEPH B., Menlo Park. Died September 13, 1971 in Menlo Park of Hodgkin's disease, aged 43. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1954. Licensed in California in 1955. Doctor Peterson was a member of the San Mateo County Medical Society.

SAMUELS, JULIUS LEWIS, Beverly Hills. Died September 13, 1971 in North Hollywood of myocardial infarction, aged 61. Graduate of Syracuse University College of Medicine, 1932. Licensed in California in 1937. Doctor Samuels was a member of the Los Angeles County Medical Association.

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SCHMIDT, HANS, San Francisco. Died August 27, 1971 in San Francisco, aged 75. Graduate of Hamburgische Universität Medizinische Fakultät, Hamburg, 1924. Licensed in California in 1953. Doctor Schmidt was a member of the San Francisco Medical Society.

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SEBASTIAN, CHARLES FRANCIS, South Laguna. Died September 3, 1971 in Laguna Beach of pneumonia, aged 76. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1922. Licensed in California in 1922. Doctor Sebastian was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

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SHELDON, EBERLE C., Hollister. Died September 10, 1971 in Corning, California, of heart disease, aged 80. Graduate of University of California Medical School, Berkeley-San Francisco, 1922. Licensed in California in 1922. Doctor Sheldon was a retired member of the San Benito County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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SMITH, DALE HANCOCK, Long Beach. Drowned August 19, 1971 while fishing in Yellowstone Park, Montana, aged 49. Graduate of University of Tennessee College of Medicine, Memphis, 1945. Licensed in California in 1960. Doctor Smith was a member of the Los Angeles County Medical Association.

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SNOW, RODNEY H., Santa Monica. Died September 28, 1971 in Santa Monica of cerebral hemorrhage, aged 74. Graduate of Northwestern University Medical School, Chicago, 1935. Licensed in California in 1935. Doctor Snow was a member of the Los Angeles County Medical Association.

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STROUSE, CARL DAVID, Torrance. Died August 25, 1971 in Los Angeles of cardiac arrest, aged 57. Graduate of the University of Chicago, The School of Medicine, 1938. Licensed in California in 1941. Doctor Strouse was an associate member of the Los Angeles County Medical Association.



Maternal and Neonatal Australia Antigen

THOMAS F. KEYS, M.D., CALVIN J. HOBEL, M.D., SUSAN RITMAN, B.S.,
WILLIAM OH, M.D., GARY L. GITNICK, M.D., AND
WILLIAM L. HEWITT, M.D., *Los Angeles*

■ *Four hundred and fourteen pairs of maternal and cord blood specimens from a county hospital population in southern California were assayed for Australia antigen by complement fixation and immunodiffusion techniques. Four maternal specimens were found to be positive (1 percent). One of the mothers with positive reaction was ill with viral hepatitis at time of delivery. Three had no evidence of symptomatic liver disease during pregnancy; two were born and raised where the prevalence of Australia antigen (Au(1)) is higher than in the United States. Although none of the cord blood specimens were positive for Au(1), one infant whose mother had Au(1) at delivery became positive at one month of age, and positive titers have persisted through 12 months of life. The significance of chronic Au(1) antigenemia in this infant is uncertain. However, it may be of importance in understanding the pathogenesis of viral hepatitis in the neonatal period.*

MATERNAL TRANSMISSION of cytomegalovirus, rubella, and herpes simplex viruses to the fetus or newborn has been clearly documented.^{1,2,3} Lack of cultural and serologic methods for identification of the viruses causing infectious and serum hepatitis has precluded similar observations in the case of hepatitis. The striking concomitance of Australia antigen (Au(1)) with human viral

hepatitis supports the concept that Au(1) may be a part of or associated with the hepatitis virus.¹ Testing for Au(1) has been useful in the epidemiologic tracing of serum hepatitis outbreaks in hemodialysis units,⁵ and is likely to be useful in screening blood for transfusions. Au(1) determinations may also be useful in demonstrating maternal transmission of viral hepatitis to the newborn. This study describes the prevalence of Au(1) in the blood of mothers delivered at a county hospital over a three-month period and correlates the presence of Au(1) in mothers or newborn or both with clinical and laboratory evidence of viral hepatitis.

From the Department of Medicine, University of California, Los Angeles, and the Departments of Obstetrics and Gynecology, and Pediatrics, Harbor General Hospital, Torrance.

Supported in part by USPHS Research Grants 1-SOL-FR-05354, 1-T1-A1-309, and the Louis B. Mayer Foundation.

Submitted June 23, 1971.

Reprint requests to: Department of Medicine, University of California, Los Angeles, Center for the Health Sciences, Los Angeles, Ca. 90024 (Dr. T. F. Keys).

TABLE 1.—*Complement Fixation Titers of Four Mothers Who Were Positive for Australia Antigen*

Case No.	Delivery	1-2 Weeks	2-4 Weeks	4-8 Weeks	8-12 Weeks	12-16 Weeks
1*	1:128	1:128	—	—	—	—
2†	1:32	—	1:64	1:64	1:64	1:64
3	1:64	—	—	—	—	1:64
4	1:16	—	1:16	—	—	—

*Acute Hepatitis

†Vietnamese Mother

—Not Tested

Methods

During a three-month period in early 1970, specimens of maternal and cord blood from all obstetrical patients delivered at Harbor General Hospital, Torrance, California were tested for Au(1). The specimens were centrifuged, the serum separated and stored at -20°C . Au(1) and anti-Au(1) antibody determinations were done by the complement fixation⁶ and immunodiffusion (Ouchterlony method)⁷ techniques. Mothers who were positive for Au(1) at time of delivery were followed. Maternal serum and serum from their infants was re-examined for the presence of Au(1). Blood specimens for determination of bilirubin, alkaline phosphatase, serum glutamic pyruvate transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) were drawn from patients who had viral hepatitis during the study and from those who were positive for Au(1). Quantitative immunoglobulin M (IgM) determinations were performed by the micro gel-diffusion method.⁸

Results

During this period 414 pairs of maternal and cord blood specimens were assayed for Au(1). Au(1) was demonstrated with the complement fixation technique in four of 414 (1.0 percent) maternal specimens but in none of the cord blood. One mother had presumption of viral hepatitis during late pregnancy while the remaining three had no evidence of symptomatic liver disease during this period. None of these specimens were positive to test by the gel-diffusion technique. None of the patients with Au(1) showed anti-Au(1) antibody.

The mother with presumed viral hepatitis during pregnancy (Patient 1) became symptomatic one week before delivery. She recalled several skin punctures from an unsterile hypodermic needle four months before the onset of her ill-

ness. Her serum was positive for Au(1) at delivery. The serum bilirubin was 10.9 mg per 100 ml (normal <1.2 mg); alkaline phosphatase was 280 milli-units per ml (normal <85 mu), and SGOT 1250 milli-units per ml (normal <45). Two weeks later bilirubin was 2.3 mg, alkaline phosphatase 170 mu and SGOT 50 mu. Although the diagnosis was not confirmed by liver biopsy, the historical and laboratory findings were consistent with viral hepatitis.

Of the three asymptomatic mothers with Au(1), one (Patient 2) was reared in a Vietnamese orphanage and another (Patient 3) had been born and reared in Samoa. The third patient (Patient 4) was a native of the United States and had grown up here. Neither Patient 3 nor Patient 4 gave a history of previous liver disease, but the Vietnamese mother recalled a generalized illness, at age 10, associated with anorexia, fatigue and loss of weight. Her symptoms subsided after six weeks of bed rest. In all three patients the results of prepartum and postpartum physical examinations were within normal limits. Serum bilirubin, alkaline phosphatase and SGPT were normal in Patient 3 three months after delivery, and normal in Patient 4 two weeks after delivery. However, three weeks postpartum, Patient 2 had SGOT of 60 mu per ml and at eight weeks had alkaline phosphatase at 108 mu per ml. Her bilirubin content was always less than 1.0 mg per 100 ml, and SGOT and alkaline phosphatase at 12 weeks were normal.

Table 1 shows the results of serial complement fixation titer determinations on the four mothers who were positive for Au(1) at delivery. The highest titer (1:128) was in the patient (unfortunately lost to follow-up) with acute viral hepatitis at time of delivery. The titers in the asymptomatic mothers ranged from 1:16 to 1:64. Significant elevations persisted three months after delivery in two patients; the third patient was lost to follow-up after one month.

Although the cord blood from Patient 2 was negative for Au(1), at one month her infant's serum became positive at 1:16 dilution. Cord blood IgM was 24 mg per 100 ml (normal 20 mg or less⁹), and when the baby was three months of age it was 64 mg per 100 ml (normal 40 mg or less¹⁰). The infant had persistent Australian antigenemia in the range of 1:32 to 1:64 during a follow-up period of one year. Results of physical and laboratory studies for liver disease were normal.

Discussion

This study demonstrates the relatively low prevalence of Au(1) in healthy mothers at delivery. It is significant that two of the three asymptomatic mothers with Au(1) were born and reared in areas of the world where Blumberg¹¹ reported a greater prevalence in apparently healthy individuals. One patient who delivered during this period had presumed prepartum viral hepatitis and at the time of delivery was positive for Au(1). Cord blood and infant blood in that case was negative for Au(1). The infant died at three days of age from prematurity and respiratory failure. There was no evidence of hepatitis in the infant at postmortem examination.

While Au(1) assays of all the cord blood specimens were negative, an infant whose asymptomatic mother had Au(1) at delivery was found to have Au(1) in his serum at one month of age. He continued to have significant Au(1) titers during his first year of life. It is possible the infant acquired Au(1) during intrauterine life, or during passage through the birth canal or by maternal contact after birth. The cord specimen and another obtained at two months of age were higher for IgM than normal for infants at this age. It is tempting to speculate that Au(1) was

acquired *in utero* and that IgM was generated by the fetus, as it is in other intrauterine infections.¹² The sensitivity of the complement fixation test may have been insufficient to detect low levels of Au(1) in cord blood.

It appears more likely, however, that Au(1) was acquired either during passage through the birth canal or by maternal contact in the external environment. Recently Schweitzer and Spears¹³ reported Au(1) in three infants whose mothers had Au(1)-positive viral hepatitis. Clinical hepatitis developed in the early postpartum period in two of the mothers and late in the third trimester of pregnancy in the other. Cord blood from the latter mother was negative for Au(1). Regardless of the mode of entry, the relation of Au(1) to the subsequent development of clinical liver disease in this interesting group of infants awaits documentation.

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A Safe Approach to Carotid Endarterectomy

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■ *One hundred twenty-four patients had 155 carotid endarterectomies for the relief of stroke symptoms. General hypercarbia anesthesia and arterial PCO₂ monitoring were used, without resort to internal bypass shunt or hypothermia. Significant permanent postoperative complications developed in three patients (1.9 percent) and there were two postoperative deaths, one of which was caused by a massive myocardial infarction.*

IT HAS BEEN ESTIMATED that 35 to 40 percent¹ of patients have "stroke symptoms" due to extracranial carotid occlusion which is accessible for vascular reconstruction. For carotid endarterectomy to gain enthusiastic support, this procedure must be demonstrated to be safe and effective in restoring normal carotid circulation. The safety of the operation depends upon the effectiveness of the measures applied to support collateral cerebral circulation during the period of ipsilateral carotid occlusion and the adequacy of the endarterectomy.

It is the purpose of this communication to consider (1) the indications for carotid endarterectomy, (2) effective methods for increasing cerebral blood flow during carotid occlusion, (3) local versus general anesthesia, and (4) the indications for the use of an internal shunt. Discussion of these problems will be based on 155 consecutive carotid endarterectomies with only two postoperative deaths and three significant permanent complications.

Clinical Material

All patients to be reported were operated upon at Loma Linda University Hospital during the period 1 July 1966 to 15 September 1969. This

clinical series is summarized in Table 1. It will be noted that the 155 consecutive carotid endarterectomies were performed in 124 patients, 31 of whom required bilateral carotid reconstruction. One patient underwent a second carotid endarterectomy for symptomatic recurrent stenosis ten months after the original operation. Eight of the operations were performed on patients who had complete occlusion of the contralateral carotid vessel.

Patients were not considered to have a significant obstructive lesion unless there was at least 60 percent stenosis of the vessel. Most patients had more than 80 percent occlusion. Approximately one-third of the plaques removed were either friable or contained thrombotic material and were thus potential sources for cerebral emboli. All but one of the occluding plaques was focal at the carotid bifurcation, as is characteristic of this disease.

The serious generalized nature of the vascular disease in these patients is evidenced by the fact that 19 percent of them had had a previous myocardial infarction, 21 percent had previously had a stroke and 47 percent were hypertensive. Despite the presence of generalized arteriosclerosis, it was surprising to observe that intracranial vascular disease was infrequently observed on angiographic examination. Twenty-five percent of the patients with significant carotid bifurcation stenosis were diabetic.

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TABLE 1.—*Clinical Series*

MALES	70
Average age	69
Range	48-85
FEMALES	54
Average age	66.5
Range	48-88
Right Endarterectomy	44
Left Endarterectomy	49
Bilateral	31

The most common indication for carotid endarterectomy was recurrent transient ischemic attacks (TIA). A TIA is defined, for the purpose of this paper, as a neurologic deficit of less than 24 hours' duration due to a disturbance in cerebral perfusion. This was the indication for carotid endarterectomy in 86 patients (70 percent). Other indications included (1) demonstration of a completely occluded carotid artery and significant stenosis of the contralateral vessel, (2) increasing dizziness, often related to the position of the head, in the presence of carotid bifurcation stenosis, (3) absence of central nervous system symptoms but significant stenosis in a patient in whom another major operation was contemplated, and (4) angiographic demonstration of an ulcerated atheroma or pronounced irregularity thought to represent a potential source for cerebral emboli.

Angiography was performed in all but one patient. This patient was treated early in the series and gave a history of allergic sensitivity to intravenous dye. A history of reaction to previous intravenous dye studies need not be a contraindication to angiography if adequate precautions are observed. A four vessel study was obtained in each patient by the percutaneous catheter technique. Biplane films of the neck and cerebral vessels were obtained by means of a Scholander film changer and a pressure injector. Cerebral angiography was simultaneously obtained in nearly all recent patients since we now recognize the importance of visualization of the intracranial "run off." Figure 1 shows a typical angiogram from a patient with carotid bifurcation disease.

It was of interest that 30 percent of the patients with significant symptoms and carotid stenosis had no bruit. This has been noted by other investigators¹ and may signify a very high degree of occlusive disease. Diminution of the carotid pulse was an unreliable physical finding since the



Figure 1.—Carotid angiogram showing pronounced stenosis at the origin of the internal carotid artery.

common carotid artery is the vessel usually palpated and the occlusion is nearly always distal to that point.

Operative Management

General endotracheal anesthesia was used in all cases. The agent most frequently employed was fluothane. During exposure of the carotid bifurcation, the CO₂ absorber was removed and the patient's pCO₂ allowed to increase to 50 to 70 mm of mercury. Arterial blood gas measurements were made routinely before occlusion to confirm the level of hypercarbia. Heparin, in a dose of 3000 to 4500 International Units was employed during the period of occlusion. Routinely the carotid arteriotomy was closed with a running 6-0 Tevdak cardiovascular suture. A small vein patch angioplasty was used only if the artery had to be reopened or if the lumen of the internal carotid artery was unusually small. A post reconstructive angiogram was routinely obtained to confirm the adequacy of endarterec-



Figure 2.—Post-reconstruction angiogram of the patient shown in Figure 1. Note that the stenosis at the origin of the internal carotid artery has been completely removed.

tomy before the wound was closed. Figure 2 shows a typical post-reconstruction intraoperative angiogram.

As the operation was done in a deliberate and unhurried manner to make certain that the distal intima was not separated from the media and that all free atheromatous debris was removed, the mean occlusion time was 21 minutes. The longest occlusion time was 55 minutes, the shortest 11.5 minutes. Re-occlusion and further endarterectomy was necessary in eight cases when intraoperative angiography demonstrated an inadequate reconstruction.

Results

Eleven patients had temporary or correctable complications. These are summarized in Table 2. Six patients had mild transient hemiparesis, usually involving only the hand, and these all cleared within one week. In three, hypoglossal nerve palsy developed but there was complete

TABLE 2.—*Transient Complications in 155 Carotid Endarterectomies*

Mild Hemiparesis	6
Hypoglossal Palsy	3
Internal Carotid Thrombosis	1
(Reoperated)	
Hematoma Requiring Evacuation	1
Total	11 (7%)

TABLE 3.—*Permanent Complications in 155 Carotid Endarterectomies*

Hemiplegia	2
Unilateral Blindness	1
Total	3 (1.9%)

return of function within six weeks. Hemiparesis due to internal carotid thrombosis developed 24 hours after operation in one patient. He was returned to the operating room for thrombectomy and an intraoperative angiogram demonstrated a widely patent carotid bifurcation and internal carotid artery. He recovered completely, without neurologic deficit. Surgical evacuation of a hematoma at the wound site was necessary in one case.

Three patients (1.9 percent) had significant permanent postoperative complications, summarized in Table 3. In one woman an unexplained but persistent hemiparesis with aphasia developed approximately six hours after operation despite the demonstration of a normal appearing carotid artery on repeat carotid angiography. Postoperative permanent hemiplegia occurred in an elderly man despite a normal post reconstruction angiogram and it is possible that embolization of atheromatous debris occurred during surgical exposure of the carotid bifurcation. The third patient had an embolism to the ophthalmic artery on the ipsilateral side 48 hours after operation and permanent unilateral blindness developed subsequently.

There were two operative deaths in this series. In one case it was because disease in the internal carotid artery was so extensive that blood flow could not be satisfactorily reestablished following endarterectomy. The patient was hemiplegic in the recovery room and died the day after operation. The second patient was doing well when a massive myocardial infarct developed on the fifth postoperative day.

Discussion

Our operative findings confirm the observation of other investigators^{2,3} that most stenotic lesions of the carotid artery are localized at the bifurcation. Fewer than 10 percent of carotid obstructions lie elsewhere and these are most frequently found at the origin of the common carotid or within the carotid siphon.² The latter lesions are not accessible for surgical correction.

The main indication for surgical intervention is recurrent transient ischemic attacks. Patients contemplating subsequent major operations (such as colectomy, gastrectomy, abdominal aortic aneurysm resection), and who have severe carotid stenosis in the absence of central nervous system symptoms should have prophylactic endarterectomy to prevent intraoperative or postoperative stroke. Patients with acute stroke symptoms should have reconstruction delayed four to six weeks, since early revascularization is fraught with the risk of postoperative hemorrhage into the area of recent cerebral infarction.^{4,5} Operation in this group will probably not significantly benefit the patient's residual neurologic deficit but may influence his future course, since if no operation is done, 20 percent will have another stroke within a year and 40 percent within four years.⁶ When total ipsilateral carotid occlusion exists, surgical reconstruction of the vessel is ordinarily unsuccessful after two weeks since the thrombus has begun organization by then and cannot be removed from the inaccessible siphon. If, however, significant stenosis exists on the contralateral side, operation seems indicated to prevent a fatal cerebral vascular accident from occlusion of the remaining functional carotid artery. Other observers⁵ have been reluctant to operate in these circumstances, but in our limited experience (six patients) and in the eight cases presented by McLaughlin et al.,³ operation was well tolerated. Transient paresis of the contralateral upper extremity was occasionally observed, but this usually cleared completely by the following day.

Stenosis secondary to elongation and kinking was rarely seen and fibromuscular hyperplasia, Takayasu's arteritis and traumatic occlusion were not observed in this group of patients. In one case significant stenosis developed at the site of previous endarterectomy, due to a decidedly thick and firm area in the arterial wall much the

same as Edwards et al.⁷ described in three patients. The cause of this complication is unclear.

Despite the rather generalized and atherosclerotic disease that was observed in the majority of these patients, and the high incidence of other systemic problems, carotid endarterectomy was very well tolerated and the complication rate was low. This is due in part to the short duration of operation, the fact that vital thoracic or abdominal organ function is not disturbed, and the early return to oral alimentation and normal activity. Cerebral vascular accident was rare after carotid endarterectomy. This can be attributed to the relatively disease-free intracranial vessels which are seen distal to carotid stenosis. It is probable that the proximal arterial obstruction protects the distal vessels from increased trauma that might otherwise occur with arterial hypertension.

Visualizing the intracranial "run off" is an important part of the procedure. In patients with cerebral symptoms and a carotid bruit, one may easily overlook such entities as a subdural hematoma, berry aneurysm or neoplasm unless adequate visualization of the intracranial vessels is obtained. Delineation of the intracranial "run off" also provides information regarding collateral circulation at the circle of Willis and is therefore of particular value in patients with multiple vessel stenosis in determining the priority for operation.

General anesthesia was used in all cases because it decreases cerebral oxygen demand by approximately 15 percent⁸ and allows smoother conduct of the operation with minimal discomfort and anxiety to the patient. It also makes possible adequate control of PO_2 and PCO_2 levels during the period of carotid occlusion. A disadvantage of local anesthesia is that the occasional uncooperative and restless patient not only increases his oxygen demand but slows the operation. Also, if the patient has been heavily premedicated, partial or intermittent respiratory obstruction and hypoxia is a possibility.

Manual carotid compression was not used in the selection of patients for operation in this series, since the results of this procedure have been demonstrated to be of little help in determining who will be able to withstand clamping of the carotid artery under general anesthesia.⁹

An internal arterial shunt was used during carotid occlusion in only four patients, very

early in the series. Such shunts are cumbersome, are likely to obscure an adequate view of the operative site, and may traumatize the distal intima. Although there may be exceptions, our results and those of other surgeons indicate that shunts are not routinely necessary.^{9,10}

All patients were given 3,000 to 4,500 international units of heparin just before occlusion of the vessel to help prevent intravascular thrombosis in an area of sluggish flow. Anti-coagulation was not continued in the postoperative period.

Various attempts have been made to increase cerebral blood flow during carotid occlusion. Most of these measures have had little beneficial effect with the exception of increased levels of pCO_2 .⁹ With pCO_2 levels between 45 and 65 mm of mercury a consistent increase in cerebral blood flow will be obtained with minimal side reactions.¹¹ At pCO_2 levels of greater than 60 mm, cardiac irritability may be noted, but this is readily reversible. The pCO_2 level is easily monitored by an arterial sample from the exposed carotid artery. Hypercarbia may be obtained by removal of the CO_2 absorber, hypoventilation, adding CO_2 to the system, or use of acetazolamide (Diamox®). We have not employed the latter, but reports by McDowell et al¹² suggest that its use for this purpose deserves further evaluation. Hypoventilation is unsafe since hypoxia may result. Increased inspired CO_2 levels or removal of the CO_2 reabsorption cannister is a simple and effective means by which hypercarbia may be obtained. We have employed the latter technique.

Moderately elevated levels of pCO_2 result in increased cardiac output, a slight increase in blood pressure, and decreased peripheral resistance secondary to the vasodilatation caused by the direct effect on the smooth muscle within the vessel wall.¹³ Blood flow to the brain^{9,14,15} as well as peripherally is increased. Other vasodilators usually have no effect on the cerebral vasculature.

Ehrenfeld and associates¹⁶ recently questioned the advisability of hypercarbia to increase cerebral blood flow during carotid occlusion. They reasoned that vessels beyond an arterial obstruction are already maximally dilated and that procedures which increase the net perfusion pressure gradient should be chosen to support circulation. They concluded that systemic hy-

pertension and hyperventilation with resulting hypocarbia should be employed for maximal brain protection. Further experimental and clinical studies will be necessary to resolve this procedural conflict.

There has been dispute in the past over the capability of severely atherosclerotic blood vessels to respond to the stimulus supplied by elevated pCO_2 levels. Now there is both clinical and experimental evidence that a satisfactory increase in cerebral blood flow can be obtained even in these patients although the onset is slower and the maximal effects smaller than in normal patients.¹⁷ Possibly this is in part due to the relative absence of significant arteriosclerosis in the vessels distal to the carotid stenosis.

In the present series postoperative carotid angiograms with injection by direct puncture of the vessel were obtained before the wound was closed, in order to verify a satisfactory endarterectomy, as has been advised by Blaisdell et al.¹⁸ Palpation of pulsation in the vessel has notoriously been an unreliable sign of patency even with the vessel exposed. Not infrequently a residual intimal flap or arthromatous debris will be visualized on the postoperative angiogram even though pulsation is entirely normal.

We believe, as do Moore et al,¹⁹ that the presence of an ulcerating atherosclerotic plaque at the bifurcation with insignificant stenosis (less than 60 percent) may be a source of emboli to the cerebral vasculature, with resultant neurological complications. On frequent occasions thrombotic or friable atherosclerotic deposits were observed within ulcerated plaques. Emboli in the intracranial circulation from such lesions may represent a significant cause of transient ischemic attack.

Simultaneous endarterectomy of the external carotid artery is important to aid in the collateral circulation to the brain via the ophthalmic artery. This is of particular importance in patients who give a history of recurrent episodes of blindness or blurring of vision on the involved side.

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Involuntary Psychiatric Hospitalization

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INDETERMINATE COMMITMENT of the mentally ill was abolished in California July 1, 1969. In its place, a variety of procedures were established for time-limited involuntary detention of certain mentally disordered persons. This system now has been in use long enough to permit an early appraisal of some of the effects.

For a number of years, mentally ill citizens of California could be committed to a mental hospital if they were dangerous to themselves or to the person or property of others, *or if* they were in need of care, supervision, treatment or restraint. The latter provision could be construed to permit wide latitude in its application. Examining physicians appointed by the Superior Court were the determiners of the person's need for care, supervision, treatment or restraint, and the criteria they used might vary from county to county and circumstance to circumstance. Counties that had a variety of community facilities that could serve mentally disordered people used the commitment laws and the state hospitals less than other counties which had fewer such facilities. There were considerable variations from one part of the state to another in the utilization of state hospital beds for elderly senile persons who were mentally disordered on the basis of organic disease of the central nervous system. Some of the counties preferentially placed such persons in the state hospital, while other counties rarely used state

hospitals for them, utilizing local nursing facilities instead.

In some counties the court review procedures in commitment cases were perfunctory; in others there were agencies which screened proposals for commitment with considerably more care.

A person committed to a state hospital forfeited a variety of civil rights—voting rights, driver's license, and professional licensure, to mention the most important. Apart from the court procedures which dealt chiefly with public hospitalization, it was possible for a person to be hospitalized in a private psychiatric hospital for a period up to 90 days solely on the basis of medical certification. Such hospitalization did not entail forfeiture of civil rights, however.

A subcommittee of the California Assembly Ways and Means Committee had been formed to deal with the general subject of mental health. This subcommittee undertook to examine the laws and procedures related to involuntary hospitalization of the mentally ill. In 1967, a preliminary document was issued by the subcommittee, entitled *The Dilemma of Mental Commitments in California*. This report condemned involuntary hospitalization procedures then in use and criticized psychiatrists and the courts alike for their participation in them. The chairman of the mental health subcommittee subsequently sponsored legislation which undertook a total reconstruction of the procedures for involuntary hospitalization. There was much debate on the underlying philosophy of the new law, as well as on the specific procedures proposed. The matter carried through two sessions in the state legislature, ending with the Mental Health Act of 1967.

The new law, as it finally emerged, besides

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setting procedures for involuntary hospitalization, included a broad revision of the state's community mental health services program which had been in effect since 1957. Even before the new law went into effect, an interim measure had been passed in the legislative session of 1967, providing that court commitment for mental disorder might be made only on the basis of dangerousness *and* the need for care, supervision and treatment, rather than on the basis of one *or* the other of these conditions.

The California Mental Health Act of 1967

As had the previous laws, the new law, known as the Lanterman-Petris-Short Act, provided for emergency detention for treatment and evaluation for 72 hours in cases where a mentally disordered person was in need of immediate detention. It also allowed petitions alleging mental disorder to be filed by relatives, friends or others. However, such petitions under the new law did not eventuate in indeterminate commitment, but only in a court order for 72-hour detention for treatment and evaluation. In other words, all involuntary hospitalization for mental disorder would now begin with the 72-hour evaluation process. This process was only justified, however, where the mentally ill person was judged to be a danger to himself or to others, or where he was judged to be gravely disabled. Grave disablement, a condition specified by the new law to cover those non-dangerous persons who were so incapacitated as to require involuntary detention, was defined as inability to provide for one's basic needs of food, clothing or shelter.

"Grave disablement" has been the thorniest aspect of the new mental health law, since its interpretation was so imprecise as to permit wide variations from area to area in its application. In some counties it has been taken to mean that the person must be so incapacitated as literally to be unable to feed, shelter or dress himself. In others it has been construed as meaning that the person is unable to carry out his normal life activities, to work at a job or to manage a household.

Once admitted for the 72-hour period of treatment and evaluation, the person may elect to remain in hospital for further treatment if he wishes to. If not, unless the preliminary evaluation confirms the judgment of dangerousness or grave disablement, he must be discharged by the

end of that period. If he is judged to be dangerous or gravely disabled, he may be placed in a facility for intensive treatment for a period not to exceed 14 days on the basis of medical certification and without a court procedure. However, since he then is being detained longer than the 72-hour emergency period without due process of law, he has to be informed of his right to contest the medical certification and to have legal assistance if he wishes to do so. If he does not contest the certification, or if he does and it is upheld, he may be held for the 14 days, for treatment.

By the end of the 14 days, if he is not discharged and does not elect to remain voluntarily, further detention in hospital can be justified in three different ways, depending on whether he is considered dangerous to himself, dangerous to others, or gravely disabled. If dangerous to himself, he may be certified *once more only* for an additional 14 days. If he is considered dangerous to others, the facility treating him may apply to the court for post-certification treatment for a period not to exceed 90 days in a facility designated for that purpose. This procedure requires a formal court hearing, and it has been very little used since the law went into effect. If the person is felt to be gravely disabled, a recommendation may be made for the establishment of a conservatorship of his person or of his person and property. This also requires a court procedure, and it is also time-limited, being for a maximum of one year. In case of dangerousness to others, both the post-certification treatment and the conservatorship can be renewed if justified, but each renewal requires a further court procedure. The intent of all this was to avoid indeterminate detention of any kind.

The looseness of the concept of "grave disablement," referred to above, has been illustrated in a practical sense by some follow-up studies done in two California counties.^{1,2} In one county, there were 345 recommendations for conservatorship during the first seven months under the new law, and 186 of the 345 recommendations eventuated in establishment of conservatorships. In the other county, only 34 recommendations were made and only 11 granted in the same period. Although the first of these counties had almost twice the population of the second, the rate

of recommendations for conservatorship per 100,000 population was almost six times as high in the first county as in the second, and the rate of granting of conservatorship was almost ten times as high. This data illustrates well the point made by Glass³ that admission procedures are determined less by laws than by philosophies.

Philosophies Regarding Involuntary Hospitalization

The issue of involuntary hospitalization of the mentally ill has been a matter of sharp disagreement and debate for many years. The motives for such involuntary detention vary from protection of the community, to protection of the ill person, to detention for the purpose of treatment; and these varying motivations are often blurred and mixed with each other. A scholarly review by Curran of commitment laws in the United States⁴ traces the history of the varying philosophies which have marked such procedures. Largely owing to the persistent efforts of Mrs. E.P.W. Packard, commitment laws in the 19th century were developed on the model of criminal procedures. Curran refers to this as the period of the "romance with the criminal law." Mrs. Packard promoted laws which were often referred to as a "bill of rights for the mentally ill." This was an interesting misnomer, since these bills were most often established to prevent the committing of persons who were not mentally ill, and they were really concerned with "innocent" people who someone might wrongly wish to have put away, rather than with those who were actually mentally ill. Curran points out that this emphasis led to a lack of concern for the treatment accorded to the mentally ill, since the only matter of concern was whether a well person might be committed. Once a person was judged to be actually ill, he might well end up in a hospital whose atmosphere was more like jail.

Moreover, this focus on procedures akin to those of the criminal law tended to cast the mentally ill into the role of wrongdoers. The reaction to this state of affairs led to what Curran calls the "romance with psychiatry" in the late 1940's and the 1950's. This reaction culminated in the 1952 Draft Act Governing Hospitalization of the Mentally Ill, which was prepared by the Federal Security Agency as a

model for state laws. It provided for informal admissions to hospitals, but it removed the legal safeguards of the earlier period, leading to a backlash from those who were concerned lest commitment laws be used for political purposes. By the mid-1960's came what Curran calls the "period of disenchantment," in which attention was paid more to what kind of treatment patients received in hospitals and to the difficulties in getting out of hospitals, rather than to the problems of getting into them.

Goffman's work⁵ provided graphic illustration of the ways in which mental hospitals were much like jails, as patients would experience them. In a less accusatory way, Smith⁶ pointed out how the logic of a custodial organization would differ from that of an organization oriented to treatment and return to the community. She suggested that involuntary hospitalization implies a kind of parent-like guardianship over the patient. The staff in a custodial institution comes to be concerned less with what is *likely* to happen as a result of some policy, and more with what might *possibly* happen. Such a focus leads to conservatism and an avoidance of risk-taking which prolongs the stay in hospital and further fosters dependency and institutionalism.

Szasz^{7,8} is more sharply critical of involuntary procedures for hospitalization of mentally disordered people, and holds that the idea of mental illness is a myth, rather than a reality. He and, more recently, Leifer⁹ suggest that our society needs to avoid admitting that it wishes to use mental hospitals to control the deviant behavior of its citizens and to preserve social order. The medical model is seen as a subterfuge to avoid that admission. Few psychiatrists would subscribe to Szasz's and Leifer's arguments in precisely the form in which they state them. However, many psychiatrists would agree that over the years the mental hospitals in the United States came to be used as custodial institutions for sequestering disturbed people, rather than as hospitals in the usual sense of medical facilities for the intensive treatment of the ill.

Roemer¹⁰ takes a more moderate position in speaking of the need to balance the patient's right to free choice with society's right to improved mental health and functioning of its citizens. She holds that the proper question is, "Under what circumstances is compulsory hospitalization justified?"

It is common for those who are opposed to compulsory hospitalization to argue that such procedures are not necessary in the case of physical illness and that they should, therefore, not be necessary in mental illness. Such arguments seem to ignore an essential difference between physical and mental illnesses: physical illnesses do not generally impair the mental functions by which a person determines a course of action. A man with a broken arm may choose not to go to the doctor. Others may deplore his decision but will generally not use other means than persuasion to change his mind. He may have a variety of reasons, sound or unsound, for his decision; but there is no thought that the fracture impairs his mental functioning or makes him unable to choose in his own best interest. In cases where organic illness impairs judgment, as where a toxic state due to organic disease causes mental confusion and judgment, what usually happens is that the confusion itself makes the person more easily persuaded to sign a voluntary hospitalization form. In such cases, no one asks whether he is mentally clear enough to know what he is doing, as would be asked in the analogous case of a confused person signing himself into a mental hospital. If a person's mental functioning is impaired by physical illness but he is not confused enough to be coaxed into signing for voluntary treatment, he is automatically placed in the category of having a mental illness due to organic brain disorder, and this places him in the category of "other" mental patients. In point of fact, many people with physical diseases who are unwilling to be treated as their doctors wish, are coaxed, bullied or frightened into "voluntarily" agreeing to be treated for their illness. Yet such coerced volunteering never seems to arouse the same concern that coercion in the case of mental illness does.

Minors, the mentally retarded and persons with senile impairment who have had guardians or conservators appointed for them are denied the right to determine whether they will be treated or not. Their parents or guardians are permitted to make that decision for them. Thus, it is clearly accepted in our society that not every person may determine whether he will be treated or not. The basis for denying a person that right is the determination on one ground or another that he is not capable of using normal

adult judgment in planning for himself. It does not seem to be so alien a concept that a person whose illness impairs his ability to make rational judgments might be as much unable to determine whether he will be treated as might a person too young, too lacking in intelligence or otherwise too impaired to do so. If mental disorders were as susceptible to cure or remission as some physical disorders, there would be far less concern about involuntary psychiatric hospitalization. It seems evident to the authors that the great concern about the matter relates to the fact that people have been involuntarily hospitalized in mental hospitals over the years without being effectively treated or returned to their homes and communities. It is the custodial atmosphere of the old state mental hospitals and the chronic incarceration of patients which makes such concerns understandable. The current focus on rapid treatment and return of such patients should lessen the concern about involuntary hospitalization.

Recent developments in England and in some other states of this country have focused on promoting informal voluntary hospitalization and establishing procedures whereby patients might protest against involuntary detention. The English Mental Health Act of 1959 replaced or modified over 50 previous acts. Laughlin¹¹ reports it is estimated that 95 percent of all patients who enter medical hospitals in England do so informally. However, Barton and Haider¹² reviewed the admissions to one English hospital in the period 1961 to 1964, and reported that 182 out of 1560 total admissions were made under a section of the law providing involuntary hospitalization in emergencies. They concluded from their review that in only 73 of the 182 cases did the record demonstrate justification for admission under the terms of that provision.

Curran¹ reports that New York, Illinois and the District of Columbia all passed laws in 1964 and 1965 emphasizing voluntary admission and abolishing civil disabilities. However, the evanescent nature of "voluntariness" is illustrated by Glass's comment³ that patients on one kind of "voluntary" admission must give 15 days' notice before leaving against medical advice, while those on another kind of "voluntary" admission must give 60 days' notice. The New York law in 1964 provided for a kind of informal admis-

sion in which a patient might leave at any time, with no coercive alternative available to the hospital. McGarry points out¹³ that Dr. Walter Barton established a similar procedure in Massachusetts in 1959, at Boston State Hospital. However, it was little used until the mid-1960's, according to McGarry.

Another feature of the New York law was the establishment of a Mental Health Information Service, which acted as a sort of ombudsman for hospitalized patients, informing them of their rights to review of their admission. Bigelow was critical of the New York law¹⁴ and especially of the provision which required the hospital physician to take the responsibility for the decision to admit the patient. This latter is, incidentally, a feature of the California law; and it was one of which many California psychiatrists were critical, since it made the hospital physician into an adversary of the unwilling patient, and was expected to make his subsequent treatment of the patient more difficult. Bigelow's estimate was that about 20 percent of patients should not be admitted on a voluntary basis. This is at some variance with the experience in England. It may represent a more conservative view on Bigelow's part, or may reflect a social difference between the two countries.

Greenland compares¹⁵ the provisions for appeal against commitment in England, Canada and the United States, indicating that a relatively small proportion of involuntarily detained patients actually pressed such appeals, and an even smaller number were ordered to be discharged as a result of such action.

Impact of the California Law

The senior author of this paper became chief of the adult inpatient service of Orange County Medical Center, the only county hospital for a county of 1.4 million people, in September 1969, two months after the new law became effective. In an attempt to monitor the effects of the law, data were collected for the month of October, 1969, and also for October, 1968. The data for the two years had been reported in differing form, making comparisons only partially feasible. It is planned to conduct a continuing study of the nature of admissions and subsequent legal status of patients in Orange County, in order to secure a sequential record of the change

TABLE 1.—*Comparison of Legal Status of Psychiatric Patients at time of Admission to Hospital, before and after Lanterman-Petris-Short (LPS) Act*

<i>Legal Status</i>	<i>Pre-LPS</i>	<i>Post-LPS</i>
Voluntary	13.3%	31%
Involuntary	61.1%	65.1%
Other	25.6%	3.9%

in legal status of patients. In future years, more complete comparisons will be possible. For purposes of this comparison, it is planned to collect data on all admissions to the hospital in October of each year. October was chosen primarily because the patients at the Medical Center are cared for by psychiatric residents, and the residents begin their training year in July. It is anticipated that by October they will have become reasonably familiar with hospital and legal procedures and will be functioning effectively.

The present paper will present preliminary data whose importance is that they represent the effect of the changes in the law for the first year under it.

Method

There were 293 admissions to the adult inpatient service in October 1968, and 235 in October 1969. The October 1968 sample will be called the "pre-LPS" (Lanterman-Petris-Short) group and the October 1969 sample will be called the "post-LPS" group.

The variables to be compared are *legal status* (that is, voluntary and involuntary), *diagnosis* and *length of stay*. These were tabulated from the Department of Mental Hygiene, Bureau of Biostatistics. Individual Patient Summary Forms 1794 and MH 1580, for the 1968 and 1969 samples respectively.

Results

Table 1 shows that the proportion of involuntary admissions did not change significantly from 1968 to 1969 but the proportion of voluntary admissions more than doubled. The change in proportion of voluntary admissions was at the expense of a category designated "other." Such admissions were not involuntary in a formal sense, but included informally "pressured" admissions such as hospital admission as a condition of probation. There is at present no way of

determining exactly how voluntary the "other" admissions were in the pre-LPS sample. For this reason, the data presented in Table 1 do not permit any firm conclusions to be drawn as to the impact of the law on legal status.

There is one other fact worth commenting on: The 1969 data permit recording of change in legal status from voluntary to involuntary and from involuntary to voluntary. Such changes were not recorded in the statistics for 1968 and the two samples cannot, therefore, be compared in this regard. In the post-LPS group, only two patients who entered voluntarily were changed to involuntary status during hospitalization. On the other hand, 35 who entered involuntarily were changed to voluntary status while they were in hospital. As to legal status at the time of discharge for the 1969 sample (post-LPS), 44.3 percent were on voluntary and 55.7 percent on involuntary status. Again, this finding cannot be compared with the 1968 sample (pre-LPS) because data of that kind were not recorded on the statistical summary sheets used in 1968.

Table 2 shows data on length of stay as related to legal status. Involuntary patients stayed for a shorter time than voluntary patients in both the pre-LPS and the post-LPS groups. Length of stay was shorter for the post-LPS group than for the pre-LPS group, both for involuntary and for voluntary patients. More than half of the

post-LPS voluntary patients stayed for six days or less, compared with less than one-third of the pre-LPS voluntary patients. In comparing involuntary patients, the proportion of those who stayed less than six days rose from 56.25 percent pre-LPS to 95.5 percent post-LPS. This finding is significant at the 0.05 level of confidence.

Length of stay in relation to diagnosis (the five major diagnostic categories) is shown in Table 3. The shift to shorter hospital stays post-LPS was noted in all categories, except transient situational reactions. In that category there appeared to be no significant change from pre-LPS to post-LPS. The most striking shifts in duration of stay from pre-LPS to post-LPS were in the schizophrenia and neurosis groups.

Conclusions

Only limited conclusions can be drawn from this first study. They are limited in part by the fact that the forms on which data were collected changed from pre-LPS to post-LPS, making comparisons uncertain. Even so, the data appear to show that the major effect of the change in the law for the first year in Orange County was to shorten the length of hospital stay for patients, and especially for involuntary patients. This change held for all the most frequent diagnostic groups except for patients with transient situational disturbances. Patients in this group stayed a relatively short time pre-LPS and post-LPS.

The data show a clear increase in the proportion of patients who were unequivocally voluntary, but this change was not accompanied by a decrease in the proportion of patients who were unequivocally involuntary. Rather, the shift appeared to be one in which fewer patients were hospitalized in categories other than clearly voluntary or clearly involuntary, and the decrease in this category was accompanied by the increase in clearly voluntary admissions.

TABLE 2.—Length of Hospital Stay for Voluntary and Involuntary Psychiatric Patients before and after Lanterman-Petris-Short Act

Number of days in hospital	Voluntary		Involuntary	
	Pre-LPS	Post-LPS	Pre-LPS	Post-LPS
6 or less	30.8%	54.75%	56.25%	95.5%*
7 to 15	38.5%	23.7%	29.8%	3.9%
16 or more	30.7%	21.55%	13.95%	0.6%

* Significant at the 0.05 level.

TABLE 3.—Length of Stay in Hospital for Psychiatric Patients of Major Diagnostic Categories, before and after Lanterman-Petris-Short Act

Number of days in hospital	Schizophrenia		Transient Situational Disturbance		Neurosis		Personality Disorders		Drug Dependence	
	Pre-LPS	Post-LPS	Pre-LPS	Post-LPS	Pre-LPS	Post-LPS	Pre-LPS	Post-LPS	Pre-LPS	Post-LPS
6 days or less	27%	72.5%	75.1%	72.3%	26%	83%	45%	74.5%	57%	73.3%
7-15 days	52.5%	9.5%	6.6%	15.3%	42.5%	8.5%	34%	14.5%	4.3%	20.8%
16 days or more	20.5%	18%	18.3%	12.4%	31.5%	8.5%	21%	11%	38.7%	5.9%

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—ROBERT A. LEVINE, M.D., Brooklyn
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Functional Aspects of the Rejection Of Transplanted Kidneys

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SINCE RENAL TRANSPLANTATION involves acts of trauma such as ischemia, denervation and ureteric mobilization and division, any assessment of the effects of transplantation per se requires information about the effects produced by each factor individually. Without this information, the clinician may be perplexed about the functional patterns presented by kidneys after transplantation. Indeed, Ogden et al (1965) stated, with little justification, "Little information is available concerning functional capacity of renal transplants." Without a great deal of information concerning the autotransplanted kidney, one is without control data and this has led to several unjustified conclusions about the behavior and morphology of allotransplants.

Control data concerning the effects of transplantation are widely scattered in the literature. Table 1 lists, in a fairly logical sequence, some details required for any reasonable assessment of the effects of transplantation. Each experiment was aimed at assessing the effect of a single factor on subsequent renal function. So far as my own experience goes, the discovery of the impaired function of a kidney autotransplanted to the carotido-jugular circulation of a dog initiated the whole investigation (Dempster 1950). It will be observed that after several procedures involving some kind of damage to the kidney a low concentrated urine in large amounts is evoked. Post-transplant diuresis was exactly the problem

which Ogden et al (1965) observed in their human cases and which initiated their own careful and critical assessment of immediate functional pattern after transplantation. It will also be seen that in some circumstances the immediate functional pattern involving a low concentrated urine continues permanently while in others normal function recovers after a few weeks.

Any control study, it will surely be conceded, must involve observations on the autotransplant. From Table 1 it is clear that up to half an hour of total ischemia causes only slight, transient functional changes and that within a few hours normal function is restored. Cutting the renal artery and vein and resuturing is followed by loss of concentration for two to six days and presumably a varying period of total ischemia accounted for these results in ten dogs. Cutting the renal artery alone and resuturing in three dogs was followed by recovery of concentration in 48 hours. Transplanting a kidney with its intact adrenal gland does not influence the early functional impairment after transplantation (Dempster 1955 b), yet a normal kidney deprived of its adrenal will continue to lose salt relative to the contralateral kidney (Dempster and Graber 1953). Sectioning and full mobilization of the ureter appears to be the key to impaired function after transplantation. The natural history of the sectioned ureter (Dempster and Daniel 1956) indicated that a mild hydronephrosis and hydro-nephrosis develop soon after sectioning and these are sufficient to impair concentrating ability for as long as the abnormality lasts.

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TABLE 1.—Assessment of the Individual Factors Involved in Early Impaired Function After Kidney Transplantation

<i>Experiment Performed</i>	<i>Immediate Function (0 hours to 2 weeks)</i>	<i>Late Function (after 4-6 weeks)</i>	<i>Comment</i>
Autotransplant kidney to neck (dog) with skin ureterostomy Dempster and Joekes (1953)	Diuresis: Hyposthenuria Salt losing GFR falls Blood flow normal	No change. Responds to anti-diuretic drugs and emotional states	Ureterostomy on skin leads to hydronephrosis at first mild and later moderate
½ hour ischemia by clamping renal artery of normal kidney Dempster (1956-57)	Normal concentration within 4 hours	Normal concentration	Transient excess protein in urine for 4 hours
Section of artery and vein followed by suture. Ureter left intact. (Dempster, unpublished)	Normal concentration in 48 hours in some cases but in others up to 6 days is required.	Normal concentration	Indicates that denervation and ½ hour ischemia are not important
Unilateral adrenal-ectomy and homo-lateral renal function Dempster and Graber (1953)	Diuresis: Subnormal concentration. Excess loss of NaCl relative to contralateral kidney	No change	No change in GFR or ERPF
Autotransplant kidney to pelvis with ureter re-implanted in bladder Dempster, Joekes and Oeconomos (1955)	Diuresis: Hyposthenuria Salt losing Blood flow } normal in ERPF } 4 hours	Normal function	Mild hydronephrosis subsides after a few weeks
Autotransplant left kidney, adrenal and ovary to pelvis. Ureter re-implanted in bladder. Dempster (1955b)	Diuresis: Hyposthenuria Salt losing Blood flow } normal in ERPF } 4 hours	Normal function	Presence of the adrenal has no effect on the impaired function
Autotransplant cooled preserved (6-20 hours) kidney to pelvis Dempster, Kountz and Jovanovic (1964) Aboul-Enein et al (1965)	Anuric or oliguric	Slow gradual return to normal function	Recovery similar to acute tubular necrosis
Allotransplant kidney to pelvis. Ureter re-implanted in bladder (Dempster 1970)	Diuresis: Hyposthenuria Salt losing Blood flow } normal in ERPF } 4 hours	Under adequate immuno-suppression normal or near normal function	Sudden decline in function starting with acute reduction in ERPF indicating rejection

The Nature of Post-Transplant Diuresis

In assessing post-transplant diuresis Ogden et al (1965) concluded that the pattern of function resembled that following the removal of obstructive uropathy in which a loss of sodium occurs. Salt loss is also associated with acute ischemic tubular damage and this factor, also, has to be taken into account in assessing the immediate post-transplant diuresis. Dempster et al (1955)

concluded that the cause of this functional pattern lay in the sectioned, denervated ureter and that edema of its wall, mild hydroureter and hydronephrosis together with some neuromuscular incoordination produced the immediate functional pattern of the autotransplant rather than an osmotic diuresis due to excess urea in which sodium loss is not characteristic (Clapp and Robinson 1969). Ogden et al (1965) found no rela-

tionship between the blood urea nitrogen (BUN) level before the transplant and the magnitude of the diuresis. The presence of urea in the proximal tubule tends to decrease sodium reabsorption so that in the uremic subject an excess serum urea contributes, to some extent, to an osmotic diuresis in the post-transplant kidney and a complicated situation occurs in which the excess sodium excretion tends to be a consequence of the urea osmotic diuresis (Maher et al 1963; Mudge et al 1949).

The Functional Pattern of the Allografted Kidney

If an allografted kidney is now substituted for an autografted kidney, the same immediate functional pattern can be observed. If the allograft is from a live donor a functional pattern similar to that observed for the autograft is seen but since the recipient is uremic the diuresis is excessive because of the excess urea, salt and water and the expansion of circulating blood volume in such patients. An expanded extracellular fluid volume is not a major factor, as the glomerular filtration rate (GFR) is frequently grossly subnormal for some weeks after transplantation. The subnormal GFR in the immediate post-transplant period requires explanation. The diuresis in such circumstances can reach 20 liters in 24 hours. It was this kind of observation which Ogden et al (1965) were concerned about since massive diuresis is clinically alarming. An osmotic diuresis due to excess electrolytes and urea will lead to dehydration unless corrected. Because a disturbance has occurred in concentrating ability, polyuria will continue when hydration is maintained. With the polyuria there will be a loss of sodium which will require correcting.

When the excess urea, salt and water have been eliminated the diuresis declines and the daily urine volume and concentration approach normal values unless acute rejection occurs which will cause a decline in all measurements of renal function. The effective renal plasma flow is profoundly disturbed first and this leads to the subsequent changes in tubular function. Once a functional pattern approaching normal is attained, any decline in function must be regarded as an indication of rejection unless proved otherwise.

The ideal conditions involved in transplanting

kidneys directly from live donors seldom occur in current practice. The function of cadaveric kidneys immediately after transplantation varies a great deal from adequate function to poor function and from oliguria to anuria lasting for several days or weeks. The total ischemia time may be greatly increased, cooling in the course of preservation at 4°C increases the renal peripheral resistance so that imperfect perfusion is not immediately achieved, and in addition there may have been a low renal blood flow for several hours before the death of the donor. All these factors create a new clinical situation after the new blood flow has been established, and one must await whatever functional pattern evolves. After a pattern approaching normal has evolved or stability at a level below normal has been reached, any decline from this base line must be regarded as indicating rejection unless proved otherwise.

The immediate functional characteristics of a successful renal pelvic autograft in a normal animal are as follows:

- Prompt excretion of hypotonic or isotonic urine in large quantities. The diuresis is probably due to impaired sodium reabsorption from the proximal tubule and this is probably linked to the mild and usually transient hydronephrosis following sectioning of the ureter.
- Reduction in the renal blood flow and effective renal plasma flow for one to four hours.
- Reduced GFR for several weeks. The GFR is usually the last feature to return to normal.
- Transient excess loss of sodium.
- Excess proteinuria lasting for some hours (Dempster 1954). The protein is derived from tubular, ureteric mucosal damage and to some extent glomerular damage. The selectivity of this urinary protein, therefore, will be poor. Electronmicroscopy demonstrates cell debris in the lumen of the tubules (Figure 1).
- Arteriograms indicate normal distribution of blood even though the total blood flow is reduced during the first few hours (Dempster 1954).

Low GFR in the Immediate Post-Transplant Phase

Immediately following transplantation, there is a short period (one to four hours) of low GFR due to a hemodynamic upset which involves inadequate perfusion of the outer renal cortex (Dempster 1971a). Adequate function continues

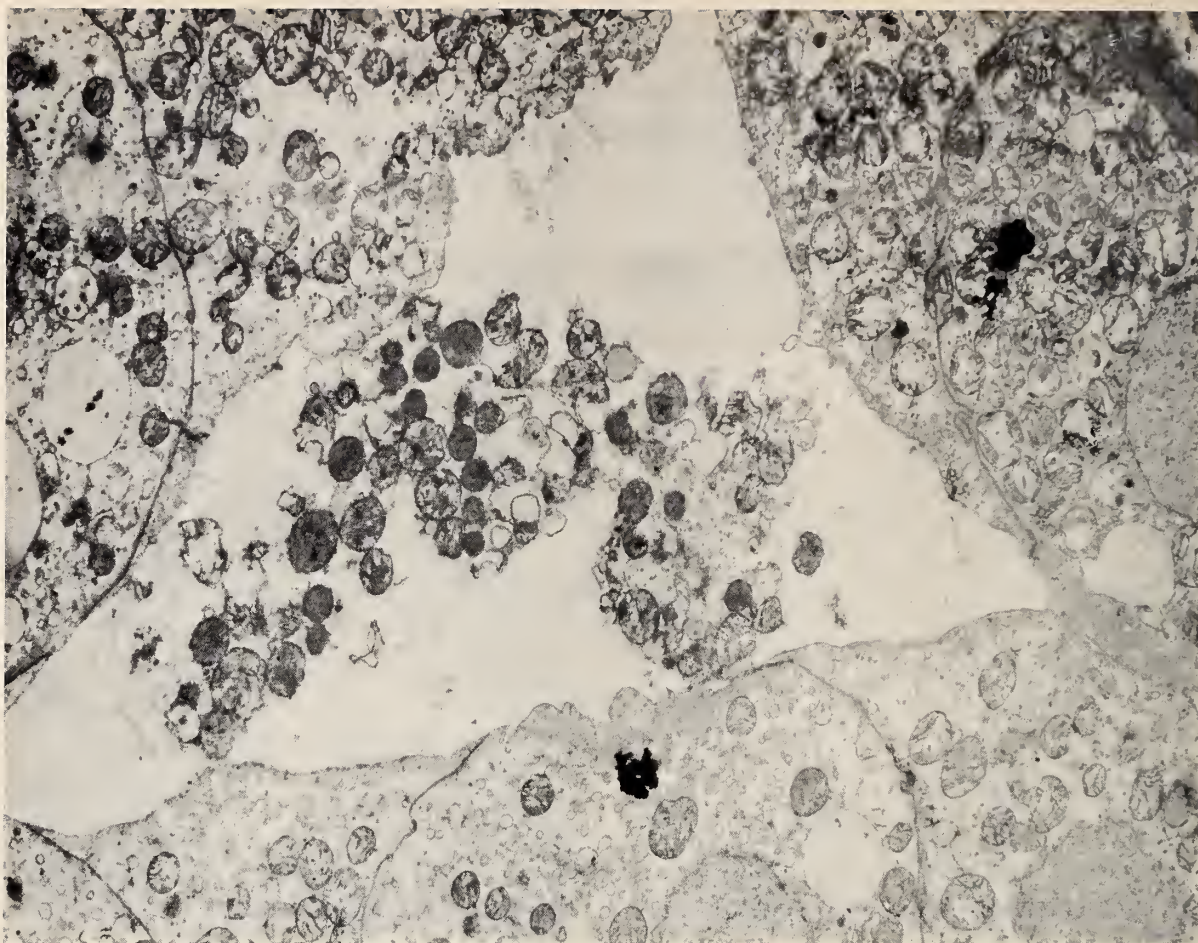


Figure 1.—An electronphotomicrograph of an autotransplanted kidney four hours after transplantation. This section demonstrates the extrusion of cytoplasmic organelles—mitochondria, lysosomes, etc., into the lumen of the tubule. This is a non-specific effect of sudden total anoxia. Reduced from x 9,750.

although there is some impairment of quality. The total renal blood flow (RBF) and the effective renal plasma flow (ERPF) usually recover to normal values within four hours but the GFR although it rises from a low immediate post-operative level remains subnormal for weeks or months. The cause of this prolonged reduction in GFR should be sought amongst those factors normally controlling GFR—glomerular permeability, capillary blood pressure, intraeapsular hydrostatic pressure and colloid osmotic pressure. Of these, the only obvious disturbance following transplantation is in the intraeapsular hydrostatic pressure. Complete ureteric obstruction will increase this hydrostatic pressure so that the GFR is reduced. Following full mobilization and section of a ureter in the course of transplantation, some ureteric incoordination and surgical trauma rather than clear obstructive nephropathy pro-

duce a mild hydroureter and hydronephrosis (Paecone et al 1965) which usually subside with the passage of time and allow the GFR to rise. If the ureter does not recover, the kidney will not recover (Dempster et al 1955).

Definitive assessment of renal function can be made only some weeks after transplantation. The functional characteristics then are—barring any rejection episodes and complications—as follows:

A return to normal concentrating ability.

A GFR which improves with time, indicating that hypertrophy is occurring or the ureteric disturbances are becoming resolved or both.

A return of normal total renal blood flow and effective renal plasma flow.

Reversal, in some cases, of diurnal rhythm.

The immediate functional characteristics of a kidney derived from a live donor and allotransplanted to a patient in gross renal failure will

depend partly on technique and partly, and usually more importantly, on the chemical state and hydration of the patient. Under optimum conditions an allotransplant will behave essentially as the autotransplant does but, in addition, the environment in which a kidney finds itself will cause adjustments so that salt and water balance will be achieved. Thus an osmotic diuresis is superimposed on the already transiently impaired reabsorptive capacity of the proximal tubule. The functional characteristics of an allotransplanted kidney at a later stage will depend on the adequacy of immuno-suppression and the presence or absence of complications. It is obvious from the data (Figure 6, Dempster 1955a) that allotransplanted kidneys vary in their ability to tolerate the changes induced by the rejection process. At four days, for example, it will be seen that some kidneys become anuric while others do not (Dempster 1955a).

The Cooled Cadaveric Kidney Allotransplant

The behavior of the cooled, preserved cadaveric kidney can be controlled, to some extent, by observing the behavior of the cooled preserved autotransplanted kidney. After a period of oliguria or anuria a recovery phase similar to the functional pattern of recovering acute tubular necrosis has been well observed.

An assessment of the function of a cadaveric cooled and preserved allotransplant to a patient in renal failure must be divided into various stages:

1. *Immediate post-transplant phase*

There may be no function for several hours, days or weeks—depending on the period of warm ischemia before cooling. During this time only a renogram can provide any information about the total renal blood flow. An arteriogram (Figure 2) will indicate inadequate perfusion of the outer cortex, and particularly spasm of the glomerular capillaries and a poor nephrogram will indicate a failure of filtration in the outer glomeruli.

2. *Onset of function*

The onset of function resembles that following acute renal failure when the diuretic phase occurs. Gradually all aspects of renal function improve and may reach normal levels but this is contingent on reperfusion of the outer cortex. Any sudden decline in

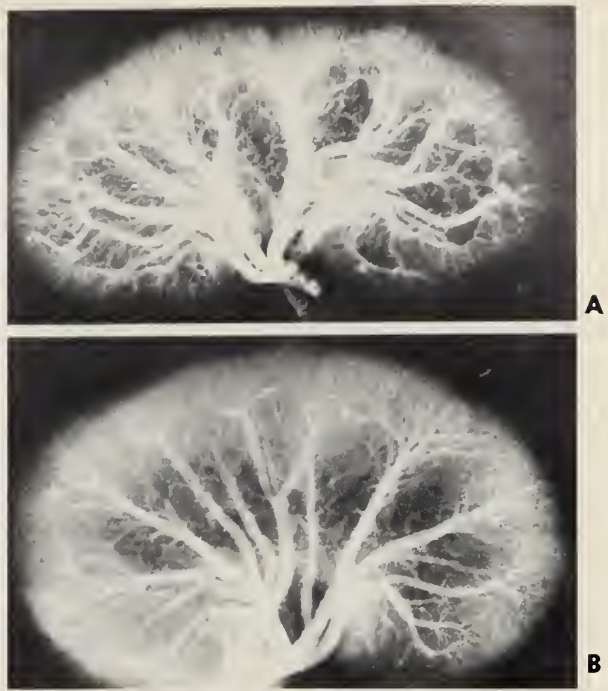


Figure 2.—Arteriogram taken 30 minutes after transplantation following preservation by cooling for 20 hours at 4°C. The perfusion of the outer cortex is poor in spite of using vasodilators. (b) A normal arteriogram of a functioning kidney 60 minutes after transplantation. The general effect of well filled glomeruli in the cortex creates a snowstorm effect as distinct from the "pallid" effect of interlobulars whose afferent arterioles and glomeruli are not being normally perfused as demonstrated in 2A.

function after this stage must be regarded as an indication of rejection unless proved otherwise. In practice, a variety of functional states evolve and these are determined by—

- a) Age of the donated kidney.
- b) Initial degree of damage before and during preservation.
- c) Any pre-existing disease in the donor kidney—pyelonephritis for example.
- d) Technique.
- e) The adequacy of immuno-suppression as reflected in the number and severity of acute rejection episodes and the ease with which they were suppressed.
- f) The degree of tolerance to immuno-suppression.
- g) The presence of urological complications—for example, urinary fistula or blockage.
- h) The nature of the renal disease of the recipient.



Figure 3.—Arteriograms of first-set allotransplanted kidneys (canine)—at various stages of rejection. (Normal, Figure 2 b). (a) Indicates early impairment in the outer cortical flow associated with profound fall in effective plasma flow and oliguria. (b) Indicates gross changes in the outer cortical flow together with total afferent vasoconstriction associated with anuria. (c) Indicates a very late phase associated with complete anuria and very low total renal blood flow.

In any long-term assessment of renal function it is frequently impossible to correlate morphol-

ogy and function. An apparently good clinical state frequently belies quite extensive parenchymal and vascular damage (Figure 3 a). The functional pattern of slow decline is that which any chronic damage to vessels and glomeruli will produce. At a certain level of damage, however, there will be a decline in overall function which will become slowly progressive. At this stage one has to consider removing the severely damaged transplanted kidney, returning the patient to the dialysis program and arranging for another transplant to be performed. The problems involved are discussed later.

Rejection—Differential Diagnosis

Rejection, acute or chronic, is the onset of renal failure due to a series of changes in the vasculature of the allotransplanted kidney leading to inadequate perfusion. The onset of acute renal allotransplant failure is the result of acute changes not only in the capillaries and venules but also in the vessels of all calibers. The onset of chronic renal allotransplant failure is the result of slow and gradual changes in the vessels, interstitial fibrosis and glomerular damage. The morphological aspects of rejection are primarily confined to the vessels, and the tubules are involved secondarily; acute tubular necrosis is associated with acute rejection and tubular atrophy is associated with chronic obliterative changes in the vessels. Similarly in the allotransplanted heart the myocardial changes are secondary to changes in the coronary vessels at all levels (Dempster 1969a). There are some limitations to descriptions such as “acute” and “chronic” in relation to rejection. The “chronic” can sometimes occur rather acutely and early and the “acute” can be sometimes superimposed on the “chronic.” Basic to all these rejection processes is increased vascular permeability (Dempster 1970).

A complete description of acute rejection requires data derived from several sources—clinical, physiological, biochemical, morphological and immunological (Table 2). Correlating these data can be quite difficult. Minimal morphological changes may occasion severe and alarming clinical signs and symptoms, and sometimes gross morphological changes are associated with

TABLE 2.—*Aspects of Acute Rejection*

Discipline	Features				
TOXIC HYPERTENSIVE SYNDROME					
Clinical	Oliguria or Anuria	Large tense painful kidney : Fever, Malaise, Anorexia : Blood cultures negative.	Increased urinary sediment : Hypertension : Urine sterile :		
Physiological	Afferent vascular spasm : Non-pulsatile flow : Acute stretching of arteries :	Decreased solute excretion :	Rapid decline in ERPF and GFR :	Relatively slow fall in total blood flow.	
Biochemical	Absolute fall in kidney enzyme levels :	Increased excretion of enzymes in urine :	Protein of poor selectivity	Progressive upset of pyruvate metabolism :	
Morphological	Vascular damage with increased vascular permeability :	Fluid loss into interstitium : mural oedema of vessels :	Cell invasion : plasma cell— endothelial cell confrontation :	Acute tubular : necrosis :	
Immunological	Cell-mediated : (small lymphocyte)	Humoral antibodies (anti-HL-A) Evidence for both processes is tenuous.			
The dilemma of first and second-set rejection					

an apparently adequate clinical state. Morphology and function are frequently not well correlated especially where chronic changes are concerned. Since any given morphological change is associated with a certain functional pattern it is obvious that a clinical diagnosis of rejection can be quite difficult. Acute and chronic rejection are consequences of acute and chronic failure of perfusion. Thus, failure of renal perfusion from whatever cause will produce a characteristic functional pattern. The onset of renal failure due to rejection has to be carefully differentiated from other causes of renal failure and other causes of a similar set of symptoms. The physiological changes recorded in rejecting allotransplants are as follows: a reduced GFR, ERPF, RBF, urine volume and solute excretion (particularly sodium); a renogram which either shows a reduced uptake or an accumulation curve. A differential diagnosis, therefore, must consider the following: renal artery stenosis, increased pressure on the renal vein and ureteric obstruction. Arteriography will certainly differentiate rejection from the other possibilities.

Acute rejection of allotransplanted kidneys can be referred to as the hypertensive-toxic syndrome (Dempster 1970). This syndrome involves oliguria or anuria, fever, anorexia and malaise; and added to these, hypertension is common (Dempster 1953b)—symptoms which are rather similar to those of pyelonephritis but the urine of the

rejecting kidney is usually sterile and blood culture of the recipient is negative.

The only feature of the toxic-hypertensive syndrome which we can surely account for is the onset of oliguria or anuria caused by afferent renal vasoconstriction (Figure 3). Fever is difficult to account for and is not due to infection (Dempster 1953b); anorexia and malaise are not due to an incipient uraemic state since these features are present in dogs retaining one normal kidney and the hypertensive state is not just due to renal ischaemia (Dempster 1970). A similar toxic state with anorexia occurs in recipients of heart transplants when rejection is in its early phase (Dempster 1969b).

Inadequate Renal Perfusion as the Cause of Functional Failure

What is the evidence that inadequate perfusion is responsible for functional failure? The factors leading to impaired renal perfusion are indicated in Chart 1. Gaps in our knowledge relate to the cause of the initial inflammatory response leading to increased capillary and venular permeability (Dempster 1970).

Increases of renal vein pressure, insufficient to induce significant change in clearance of PAH and creatinine, result in a large percentage decrease in sodium excretion and urine volume. A decrease in perfusion pressure will reduce solute excretion proportionately with the reduction of

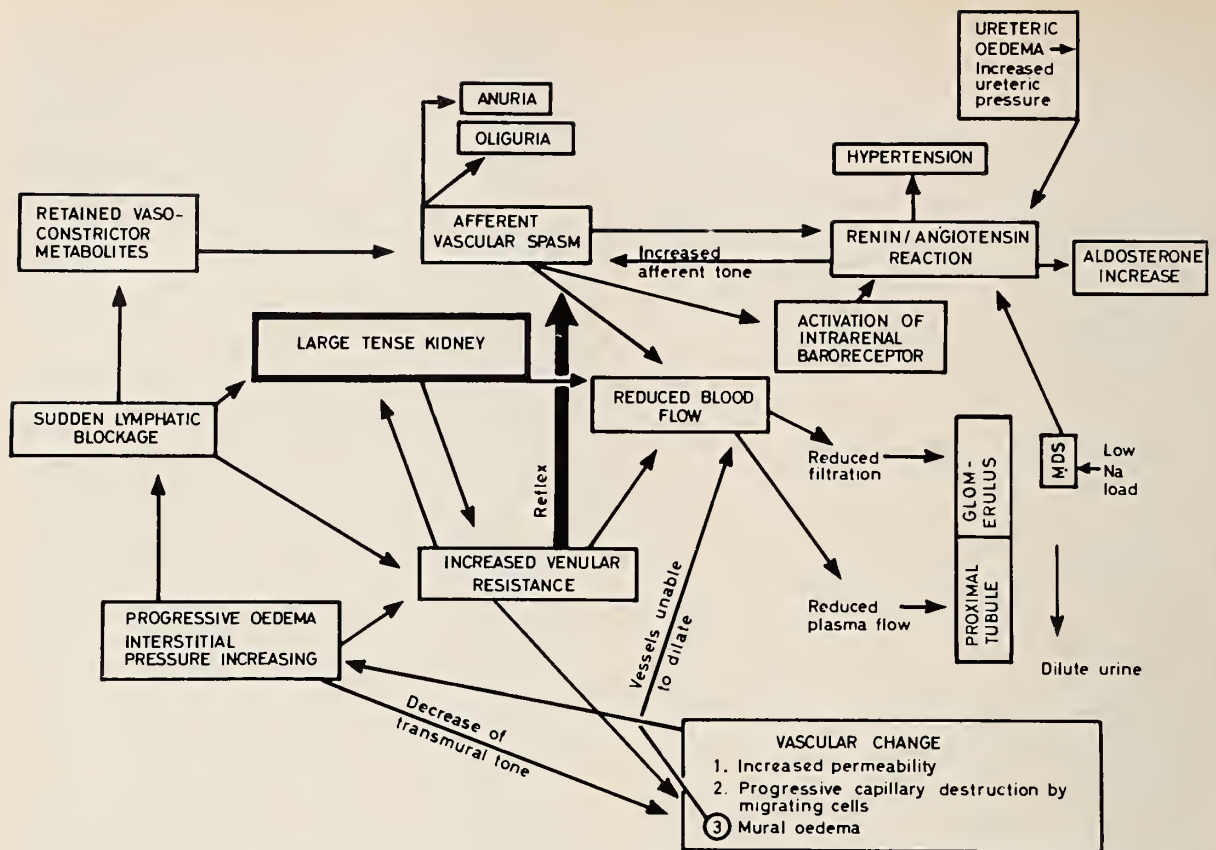


Chart 1.—The scheme demonstrates the effects of increased vascular permeability on renal hemodynamics of the first-set allotransplanted kidney. (Dempster W J, 1970: Brit J Exp Path 51:149, 1970).

GFR after a certain stage of arterial constriction. With minimal decrease in arterial pressure, reductions in excretion of Na and the urine volume occur before any changes in renal blood flow and GFR are detected.

Alterations in perfusing pressure or renal vein pressure are rapidly progressive in a kidney about to undergo acute rejection. Thus, there is seldom time enough to detect a sharp fall in sodium excretion before any detectable decline has occurred in GFR and ERPF. Usually, by the time a routine assessment is made all factors have declined. It is perhaps an unattainable ideal to expect to detect a single change in functional pattern which is well in advance of other parameters of function.

If kidneys are examined during the phase of acute rejection it will be observed that the hilar fat surrounding the renal vein is extremely edematous (Dempster 1970—Figure 5). Pressure by this edematous area surrounding the renal vein may be the first cause of the fall in solute excre-

tion. The next phase involves an increase in venular pressure due to a rising interstitial pressure. At a certain critical stage afferent vasoconstriction is produced and the perfusion pressure in the outer cortex falls. This will lead to reduced solute excretion, reduced urine volume and a precipitate fall in ERPF. Should any other hemodynamic upset be required a raised ureteric pressure due to edema and compression at the site of anastomosis can be added to the above factors.

These conclusions are derived from experiments lasting a relatively short time. Rejection is a process involving a progressive decrease in renal perfusion and a measure of this factor is central to any diagnosis of acute rejection. The 15-minute Phenol Red Test is cheap, easy, accurate and repeatable. In our early observations (Dempster 1953a) it was found that the total renal blood flow was very low at the stage of anuria. It took some time to realise that the onset of rejection coincided with oliguria and that anuria was a much later feature of rejection. If

the total renal blood flow is measured at oliguria it may be found that there is no statistical fall before the crisis of frank rejection (Dempster 1967). If the blood flow is measured at other intervals during the functioning phase no apparent gross decline in flow can be recorded. Also, for a few hours after transplantation total blood flow may be 50 percent of normal and yet there is usually an adequate urine flow because the distribution of blood is normal (Dempster 1954). The difference between this early low flow and the flow at the time of oliguria and anuria is one of distribution of total flow. Rejection is associated with not only a fall in total renal blood flow but also with a change in its distribution so that the outer cortex is deprived of perfusion. Vasoconstriction of the afferent system appears to be responsible, and once vasoconstriction occurs the total renal blood flow declines relatively slowly but the effective renal plasma flow falls profoundly and suddenly. Arteriography at this stage of rejection will reveal outer cortical ischemia and generalized afferent spasm (Dempster 1955a). There will now be an oliguric phase with delayed passage of contrast material through the kidney. By the time anuria is established the total renal blood flow will have fallen considerably. Later the values for total blood flow are virtually those that could correspond to medullary flow alone (Dempster 1953a; Jackson and Mannick 1964). Because total renal blood flow in such conditions can be reduced to 10 percent of normal and hence approximately the value for medullary flow, it would be misleading to conclude anything about the state of medullary flow. China ink injections reveal, in such vasoconstricted kidneys, that medullary flow is decidedly reduced whenever outer cortical flow is reduced (Dempster 1971a). What causes the vascular spasm?

Due to progressive leakage of fluid a stage is reached when the increased interstitial pressure causes increased venular resistance. This appears to precipitate afferent vascular spasm. This can be experimentally produced by constricting the renal vein of an allotransplanted kidney. If the renal vein constriction is released at the end of an hour a reversal of flow occurs and allows normal perfusion of the outer cortex (Dempster 1970). The exact cause of raised venular resistance and afferent vascular spasm has not yet been defined.

Non-Pulsatile Flow in the Renal Artery

Soon after the onset of afferent vascular spasm the flow along the extrarenal portion of the renal artery becomes non-pulsatile (Dempster 1955a; Henry et al 1969). Depulsation is known to depress tubular excretory function (Many et al 1967). The onset of non-pulsatile flow is not entirely connected with increased peripheral resistance because in early anuria of whatever cause, in second-set reactions or in immediately anuric cadaveric kidneys pulsatile flow along the renal artery as far as the arcuates continues for 24 hours or more. With reversal of rejection pulsatile flow in the renal artery returns simultaneously.

Sudden Anuria Due to Thrombosis or Rejection

Renograms taken during acute rejection are not very revealing since they cannot differentiate the various causes of any deformity of uptake or excretion phase. Renograms will not clearly demonstrate the distribution of blood which is all important. Thus, although a more traumatic procedure, arteriography, when well performed, can be a greater aid in diagnosing rejection. This procedure, however, is hardly necessary in a patient who is ill and in whom other features of rejection can be more easily measured. Serial osmolalities, for example, can be valuable in arriving at a differential diagnosis. If the osmolality has been near normal or has been stabilized at a certain level and the last value before anuria continues the previous trend, one can diagnose renal artery thrombosis. If, however, the final osmolality before anuria reveals a value much lower than the preceding values, a diagnosis of rejection is reasonable since the acute rejection process, in its early stages, involves inadequate renal perfusion and hence a pronounced decrease in solute excretion.

Late or Chronic Rejection

Metabolic studies of allotransplanted kidneys are limited by the linked nature of metabolic pathways to the fundamental pyruvate stage. Any disturbance here (Dempster and Kountz 1966) will have far-reaching effects. Recently O'Brien et al (1970) reported early disturbances of phospholipid metabolism and fatty acid oxidation which would fit earlier disturbances at the pyruvate stage although this may be difficult to

demonstrate. It should be realized that all kidneys rendered totally anoxic for a period up to 60 minutes at body temperature reveal physical damage to the tubule cells which is reversible. It is possible that the allotransplants, in a proportion of instances, cannot replace the lost organ-elles quickly enough.

Glomerular Changes

In the immediate post-transplant phase the GFR can be decidedly reduced without detectable signs of damage. We have previously ascribed this to ureteric incoordination which can result in some upset in glomerulo-tubular balance. However, the decreased GFR, per se, may not be the main factor in the glomerulo-tubular balance which is controlled by several factors—(1) tubular volume which influences the reabsorptive state, (2) the rate of removal of fluid from the peritubular interstitium into the capillary network which is sensitive to variations in colloid osmotic pressure and the hydrostatic pressure within the capillary, (3) the perfusion pressure, any small decrease of which can decrease sodium excretion without changing GFR, and (4) excess aldosterone secretion due to stress will inhibit sodium and so water excretion. Of these, the most important is perfusion pressure, which appears to be decreased due to increased renal peripheral vascular pressure (Dempster 1970).

In acute rejection soon after transplantation, the glomeruli are usually characteristically normal in histological sections. In rejection occurring some months after transplantation glomerular damage is very common although probably not the main cause of renal failure. The extent of the glomerular damage varies and may lead to the onset of the nephrotic syndrome, when doubly refractile lipid bodies are detected (Harlan et al 1967). Other investigators deny that transplant proteinuria ever evolves into nephrosis.

Live donor kidneys leak protein immediately after transplantation and this lasts several hours (Dempster 1954). This has been attributed to ischemic damage to the tubules and is of poor selectivity. From then on, proteinuria of poor selectivity will reappear during phases of acute rejection where conditions involving inadequate perfusion prevail. What causes the glomerular changes that appear some weeks or months after transplantation remains obscure. In some in-

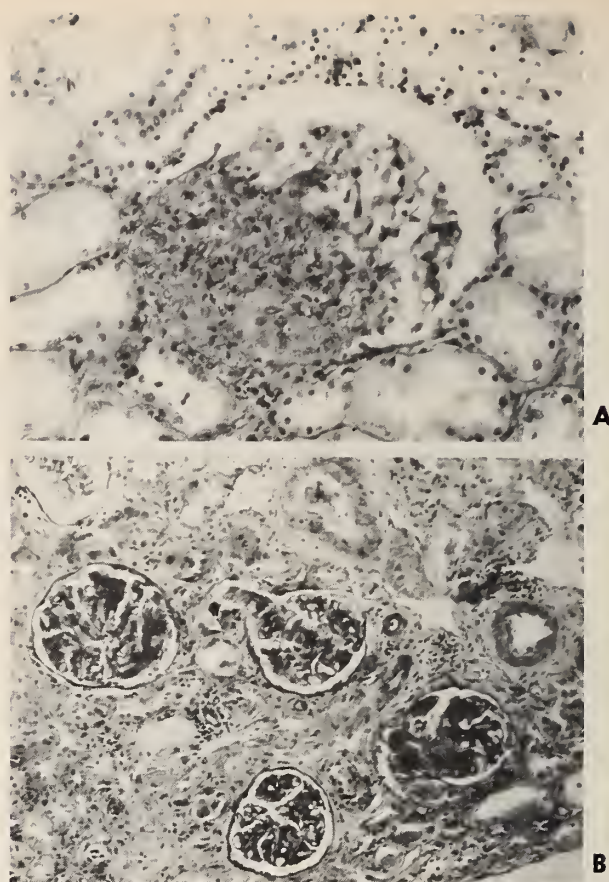


Figure 4.—Photomicrographs of glomerular lesions in human first-set allotransplanted kidneys associated with an adequate general clinical state. (a) A glomerular lesion closely resembling focal glomerulonephritis (Heptinstall & Joekes 1963). Picro-Mallory x 160. (b) Glomerular lesion involving large fibrinoid deposits in about 40 percent of glomeruli associated with a GFR reduction of 60 percent. Picro-Mallory x 160.

stances the glomerular changes represent a recurrence of a preexisting glomerulonephritis and in others it would seem that transplantation antigen-antibody complexes are responsible. Although subepithelial deposits and humps are commonly found in cases of membranous and post-streptococcal glomerulonephritis and sub-endothelial deposits and humps are found in some cases of kidney allotransplants, a differential diagnosis of subendothelial deposits involves a consideration of causes such as nephrotoxic serum, acute glomerulonephritis, lipid nephrosis, lupus nephritis, diabetic nephropathy, chronic glomerulonephritis, anaphylactic purpura, and nephrosclerosis.

Although glomerular changes can present, microscopically (McKenzie and Whittingham 1968),

TABLE 3.—*Aspects of Late or Chronic Rejection*

Discipline	Features
ACUTE SYMPTOMS IF ACUTE REJECTION IS SUPERIMPOSED	
Clinical	Hypertension : Anemia : Progressive decline in well-being as progressive decline in renal function develops : Infections : Bone disturbances.
Physiological	Progressive decline in GFR, solute excretion, ERPF and total renal blood flow.
Biochemical	Progressive increase in urinary sediment—tubular casts, enzymes, cells of all types. Protein of poor selectivity
Morphological	Progressive vascular obliteration : Interstitial fibrosis : Edema : Glomerular damage Tubular atrophy : Cell invasion of variable proportions.
Immunological	Recurrent glomerulonephritis Antigen-antibody complex glomerulonephritis Cell-mediated or humoral antibodies (anti-HL-A) or a new unknown complex.

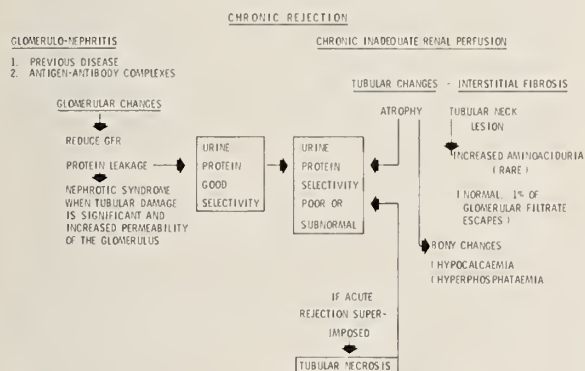


Chart 2—Chronic Rejection Process

an alarming appearance they are frequently accompanied by quite adequate renal function (Figure 4 b). A lesion resembling focal glomerulonephritis, as described by Heptinstall and Joekes (1963) can be observed in a human kidney following allotransplantation (Figure 4 a). It is rare, however, for allotransplanted kidneys to show glomerular changes without at the same time showing developing interstitial fibrosis and the obliterative vascular lesion. For this reason proteinuria will always be of poor selectivity so that this test is seldom of real value. It is the rate and extent of the obliterative vascular lesion which is going to dictate how long the kidney will continue to function adequately. In the long run, the vascular lesions will lead to gradual tubular atrophy and chronic renal failure (Table 3, Chart 2); and, indeed, one is frequently amazed at the extent of morphological damage commensurate with an adequate clinical state. The GFR, however, can be reduced by 66 percent without necessarily upsetting glomerulo-tubular balance.

Tubular Changes (Chart 2)

Ischemia probably causes the necrosis of cells in the neck of the proximal tubule (Figure 5) (Darmady et al 1956). Although this lesion resembles an acute form of the "swan neck" deformity observed in Fanconi syndrome, no evidence of increased aminoaciduria was found during acute rejection. In only one human case (Massry et al 1967) has increased aminoaciduria been described, and that under conditions which are difficult to assess. Several tubular functions were depressed, particularly an inability to excrete hydrogen ions which is characteristic of the "neck" autotransplanted kidney, but without excess aminoacid excretion.

Disturbance of Tubular Transport Calcium-Phosphate Relationships

Calcium-phosphate bone interrelationships become progressively disrupted in renal disease. After renal transplantation the various chemical abnormalities of uremia are quickly corrected but parathyroid involution does not always occur and may require surgical intervention. When GFR falls below 25 to 30 ml a minute, hyperphosphatemia occurs and this stimulates parathyroid hormone (PTH) release. Steroids tend to protect against the development of hyperphosphatemia but care must be taken to ensure against hypercalcemia. Abnormalities in vitamin D metabolism may be reversed after renal transplantation and absorption from the gut becomes more efficient and, in the absence of steroids, may predispose to the development of hypercalcemia and nephrocalcinosis.

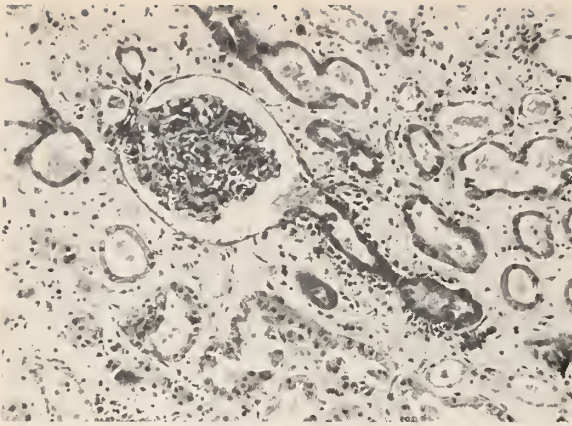


Figure 5.—Photomicrographs of a section of human allotransplanted kidneys rejected acutely. Debris in Bowman's space consists of fragments of neck tubule cells. Hematoxylin-eosin stain x 90.

Interstitial Changes—Fibrosis

The cause of interstitial fibrosis is probably long-standing interstitial edema. Collagen is frequently observed in the vicinity of plasma cells lying in the interstitium. There are perhaps two factors, then, leading to the laying down of collagen which eventually leads to tubular atrophy and death of tubules—focally. This will, in turn, lead to proteinuria of poor selectivity and hence is of some diagnostic value in that it indicates that tubular as well as glomerular damage has occurred.

Renal Vascular Changes

Renal vascular changes include increased permeability, intertubular capillary and venular disorganization by circulating plasma cells and an obliterative process involving vessels of all sizes but mainly the interlobular. Terms such as acute and chronic vascular lesions do not accurately reflect the tempo of the latter two disease processes in the immuno-suppressed human. These processes frequently are associated together in the rejection episodes soon after transplantation. The obliterative lesion can be very acute and capillary disorganization can be superimposed on the more chronic obliterative lesion and evoke, clinically, an acute rejection episode. Chart 1 indicates the pathophysiological result of a combination of renal vascular changes in an allotransplanted kidney. Once vascular permeability is increased and is not kept under control, hemodynamic changes will occur which lead to afferent renal vascular spasm. Sudden failure to

perfuse adequately the outer cortex can account for the renal failure of an acute rejection episode. Vascular function may only be impaired to the extent that the larger vessels are unable to dilate on demand due to the intramural edema. The ability to dilate on demand is the most important function of an artery. There is quite a range of arteriographic patterns, depending on the strength of the rejection process and the time when the arteriogram is made.

A reversal of rejection involves a reversal of the afferent arterial spasm, particularly the exclusion of the outer cortical circulation (Figure 3). The rationale for using large doses of hydrocortisone to reverse rejection is now clear, since this drug acts by stabilizing vascular permeability and so allows flow to return to the outer cortex with subsequent recovery of renal function. However, as a result of the temporary rejection episode certain sequelae follow which will be discussed later.

Division of Labor Among the Nephrons

Since the outer cortical glomeruli and nephrons are particularly involved when the cortical spasm occurs, some attention should be paid to the suggestion (Barger 1966) that the tubules supplied by the outer cortical glomeruli are adapted to salt excretion. A diagrammatic representation of the cortical vessels has been presented by Barger which suggests that the classical view of the arrangement of the outer cortical vessels is not correct. The diagram suggests that special vessels arise from the arcuates and proceed to the outer cortex without giving off afferent arterioles until they reach the outer cortex—something in the manner of branches at the tops of coconut trees. Spasm of these vessels, it is suggested, will considerably reduce the excretion of water and salt. In a prolonged search, I have not been able to detect such vessels in neoprene casts of kidneys (Dempster 1971b). Nevertheless, there is some other evidence to support the interesting suggestion that tubules arising from the glomeruli of the outer cortex are concerned in salt excretion (Horster and Thurnau 1968; Dempster 1971b).

Hypertension as a Sign of Rejection

As a sign of rejection, hypertension is fairly common. The cause is rather obscure and evidence for a renin/angiotensin involvement is lacking. Hypertension following transplantation,

of course, can be due to causes other than rejection—glomerulonephritis in the kidneys of the recipient, fluid and salt imbalance, excess steroids, stenosis of the renal artery due either to stricture or rejection disease.

Hypertension associated with rejection occurs in both acute and chronic rejection and it is rather doubtful if the same mechanism operates in both processes. There has been some difficulty in correlating blood pressure, plasma renin activity and aldosterone secretion during rejection episodes in allotransplanted kidneys. It was originally considered that hypertension during rejection was due to renin release in an ischemic kidney which was demonstrated by arteriography and renal blood flows (Dempster 1953b). Sometimes hypertension is not present during rejection, either in dog or man, and this is just as mysterious as when it is present, since ischemic or rather underperfused kidneys are common to both clinical conditions. Though the renin content of a kidney is reported to be reduced by denervation and steroids (as in kidney allotransplantation presumably) there appears (in a large proportion of rejection episodes) little interference with the mechanism which allows hypertensive states to be reached.

Plasma renin activity is probably raised because there is some impairment of perfusion of the outer cortex following the afferent spasm. However, this raised plasma renin activity may not be associated with a raised blood pressure. It has been argued (Dempster 1970) that since the renin/angiotensin system does not explain the hypertension of rejection it may be that rejection in some way inhibits a hypotension-promoting mechanism in the kidney.

Proteinuria as a Sign of Rejection

Protein excreted in quantities greater than 3.5 grams per 24 hours per 1.73 square meters of body surface occurs in both acute and chronic forms of rejection. This increased proteinuria is usually of poor selectivity because tubular damage and ureteric mucosal damage is involved. Very rarely does glomerular damage occur alone, and so a proteinuria of good selectivity rarely occurs. Excess proteinuria may proceed to frank nephrosis in some cases but some units report that they have not encountered this complication. Nephrosis has been diagnosed on the basis that

lipoid bodies as well as protein appeared in the urine. Histuria (Antoine et al 1969) is well correlated with gross interstitial and tubular damage.

Microvascular Angiopathic Hemolytic Anemia (MAHA) as a Sign of Rejection

It is not clear from other disease processes involving MAHA what the cause is although fibrin strands have been suggested by some investigators (Bull et al 1968). Since during rejection the capillaries and venules of allotransplanted kidneys are often under attack and laminar flow is disturbed, it might seem that the scene is set for damage to red blood cells from this source alone. The red blood cell in dogs appears to be more fragile than in humans, and perhaps this may explain why MAHA is relatively rare in the human rejecting allotransplanted kidney (Lichtman et al 1968). When it does occur it is a very late sign and, indeed, it is debatable whether rejecting kidneys should be retained until so late a stage.

Oliguria or Anuria in the Immediate Post-Transplant Period

The recent interest in so-called hyperacute rejection has been bedeviled by too enthusiastic a use of immunological catch-phrases, like Shwartzman reaction and Arthus reaction, employed usually without any reference to the theoretically necessary prerequisite of a hypercoagulable state or fibrinolysis. Another factor contributing to confusion is that few clinics have studied this problem experimentally. In several respects dog and man are not similar from an immunological point of view. Nonetheless, reports of immediate post-transplant anuria in human second kidneys from different donors (Williams et al 1969) are sufficiently close, from a clinico-pathological point of view, to earlier observations of second-set canine kidneys (Dempster 1953a, 1969a) that at least a start can be made by formal experimentation on dogs, followed by an assessment of what is common to the human situation. My object now is to try to set out the conditions under which one may so classify any given immediate post-transplant anuria as a second-set rejection or, as it is loosely referred to, *hyperacute rejection* (Kissmeyer-Nielsen et al 1966).

The current evidence against a Shwartzman-type of reaction occurring in those so-called hy-

peracute rejection is as follows: (1) No evidence of previous hypercoagulability (Pineo et al 1970) and this agrees with some human evidence (Colman et al 1969). (2) The non-specificity of polymorph margination evoked by any severe hemodynamic upset (Dempster 1969a). This rules out the suggestion of Clark et al (1968) that polymorphs are effectors of rejection. (3) The failure of Arvin to influence a second-set rejection (Pineo et al 1970) indicates that intravascular coagulation plays a minor role in the second-set reaction. Detection of fibrin within a kidney is significant only in relation to the events preceding its deposition. In any severe renal hemodynamic upset, fibrin will be deposited but this does not reveal what has precipitated the hemodynamic crisis (Dempster 1969a). (4) The Schwartzman reaction is dependent on functional defects of the reticulo-endothelial system and the second-set reaction is not. (5) The Schwartzman reaction is abrogated by denervation but the second-set reaction is not. (6) The severity of the Schwartzman reaction is reduced by phenoxylbenzamine but this has no effect on the second-set reaction. (7) Decomplementation has no effect on the second-set reaction (Dempster and Brown 1971) and this makes it highly improbable that HL-A antibodies, which are dependent on complement fixation—*in vitro*, at least—as the mediators of second-set rejection.

There are, of course, similarities between the generalized Schwartzman reaction and the second-set kidney transplant reaction viz:

1. There is glomerular dilatation with stasis in the early phase before fibrin deposition (Dempster 1953a; McKay and Rowe 1960).
2. Vasomotor disturbances lead to increased venular resistance and afferent vasoconstriction (Dempster 1953a; Schneider et al 1968; Pineo et al 1970).
3. In the late phase there is glomerular contraction and fibrin deposition (Dempster 1953a; Pineo et al 1970).

The Detection of Renal Deposited Fibrin and Fibrinuria as Tests of Rejection

Fibrin and fibrinogen are not normally detectable in urine. Antoine et al (1969) proposed the term *fibrinuria* to denote the presence of fibrinogen-like material in the urine from human transplanted kidneys. Although fibrinuria is a constant feature in the early post-transplant phase,

it is due to several varied causes. Two main conclusions emerge from their work: (1) There is a close correlation between high steroid dosage and fibrinuria, and (2) when renal deposits of fibrin have been proved, fibrinuria is sometimes absent.

Fibrin or fibrinoid can be detected in second-set rejections (Dempster 1953a, Pineo et al 1971) and first-set rejections of the vascular obliterative type. Fibrinoid deposits in the glomeruli and afferent arterioles and interlobulars are constant in second-set rejections but only occasional and focal in first-set rejection. McKenzie and Whittingham (1968), for example, detected focal deposits of fibrin in only 32 percent of rejecting first-set kidneys. In late onset first-set rejections, Porter (1967) detected fibrinogen in 17 percent and this was accompanied by IgM. The detection of fibrin under the conditions reported by these investigators indicates that fibrin deposition is the end-result of a process which disturbs the vascular endothelium and intima and together with a preceding increased vascular permeability evokes an afferent vasoconstriction, leading to underperfusion of the outer cortex. If, as Antoine et al (1969) reported, fibrinuria does not occur in a proportion of such cases, it is possible that this is because glomerular filtration of the affected glomeruli has stopped. Underperfusion of the cortex would certainly lead to some degree of renal failure.

Why fibrin should be deposited in first-set transplanted kidneys undergoing acute classical rejection is not easy to understand because of past difficulty in demonstrating fibrin or fibrinoid by histochemical means. Salaman (1970) reported increased ¹²⁵I-fibrinogen radioactivity in transplanted kidneys during acute rejection and the biopsy illustrates that acute classical rejection was considered to be the diagnosis. After the transplantation of a cadaver kidney and immediate anuria, a biopsy is limited in allowing one to arrive confidently at a diagnosis of acute rejection as against a similar lesion found in most cases of acute renal failure. Unless a biopsy includes interlobular arteries, in which case there is usually severe bleeding, fibrinoid necrosis can be missed and the damage to the tubules of the outer cortex assumed to be due to ischemia alone (Figure 6 a, b).

Pineo et al (1970) detected protein-bound radioactivity in the urine from both normal and

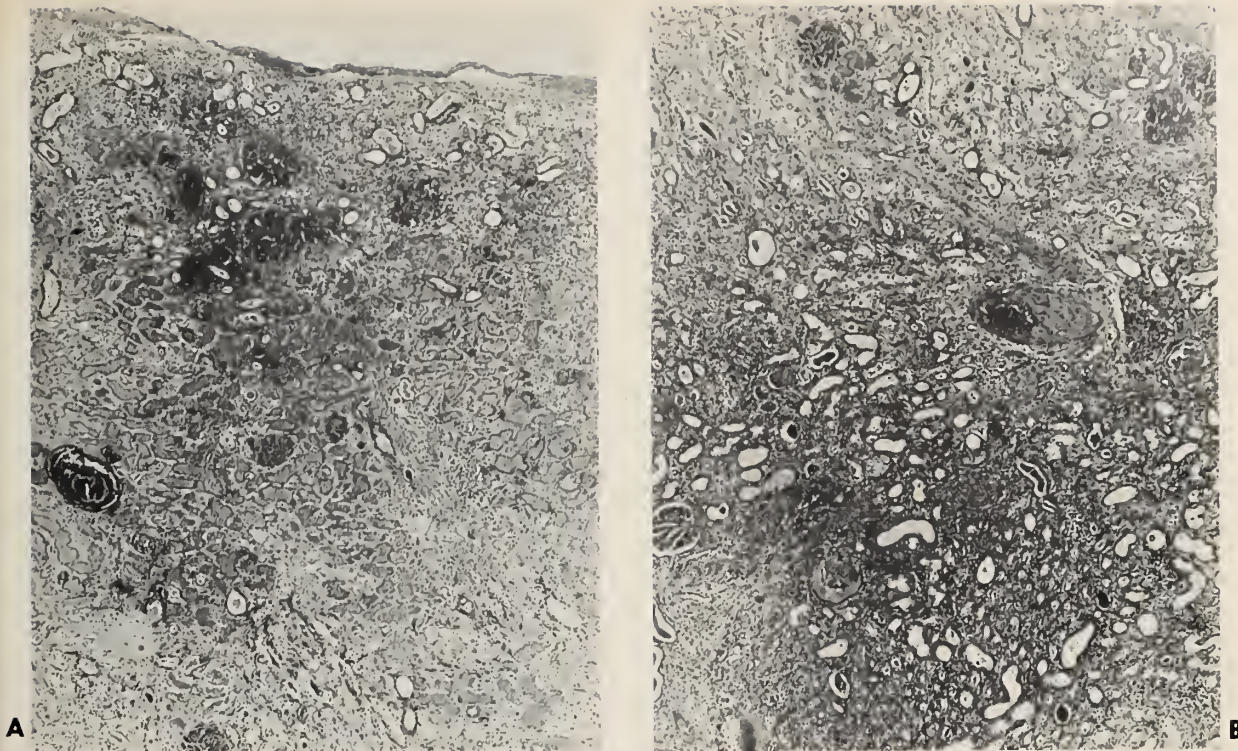


Figure 6.—(a) Section of a human cadaveric first-set transplant removed after 10 days without functioning. The outer cortex resembles the features of cold ischemia same kidney but photographed a few mms. further into the cortex. The obliterative vascular lesion of an interlobular is now clearly demonstrated. The diagnosis of ischemic damage followed later by the early onset of the obliterative vascular lesion in which fibrinoid necrosis occurs in the early stages. Picro-Mallory x 80.

rejecting second-set allotransplanted kidneys in any given animal. Like the fragments detected by Antoine et al (1969), the radioactivity was bound to high molecular weight protein but the significance is not understood although the excretion of such substances denotes increased vascular permeability, known to be present early, rather than local fibrinolysis. Since plasminogen levels were the same in renal and peripheral circulations, it would indicate that local fibrinolysis is not occurring at an increased rate. The conclusion appears to be that systemic coagulation plays no role in second-set rejections and intrarenal coagulation follows severe vasomotor disturbances within the kidney which are fundamentally responsible for the onset of acute renal failure (Pineo et al 1970; Dempster 1971). Colmen et al (1969) came to a similar conclusion in rejecting the concept that hyperacute rejection was an analogue of the generalized Shwartzman reaction. It should be pointed out, however, that to claim a primary role for coagulation in the

Shwartzman reaction is debatable since it is suppressed by renal denervation, reduced in severity by phenoxybenzamine and is dependent on functional defects of the reticulo-endothelial system. In a more recent assessment of immediate post-transplant anuria, Starzl et al (1970) withdrew their previous view that the second-set kidney transplant reaction was a Shwartzman reaction. Their assessment is now close to the original view expressed by Dempster (1953a).

Hyperacute Rejection— A Second-Set Reaction or Not?

Without adequate controls involving hemodynamic upsets due to hemoconcentration or hypovolemia in autotransplanted kidneys, one is in some difficulty in assessing the immunological significance of anurias designated "hyperacute rejection." At best, hyperacute rejection is better known as second-set rejection—that is, the reaction which occurs when an animal is sufficiently sensitized by a rejected and once viable trans-

plant and a sufficiently long interval of time has been allowed to elapse before the animal is challenged again with a kidney allotransplant. It is by no means clear, in many cases, whether hyperacute rejections are second-set rejections or not. Except for the reports of Williams et al (1969) and Nakamoto et al (1967) on the fate of a proportion of second kidney transplants from different donors, a technical factor—hypovolemia or poor preservation, for example—could explain the immediate post-transplant anuria which is a less dogmatic term than “hyperacute rejection.” Evidence for pre-existing HLA antibodies may (Kissmeyer-Nielsen et al 1966) or may not (Turcotte et al 1970) be associated with irreversible anuria. The reports of hyperacute rejection incriminate previous sensitization by pregnancy antibodies or blood transfusion antibodies. This, in effect, incriminates the leukocytes as sensitizers but these cells have failed, experimentally, to sensitize recipients against kidney and heart transplants (Calne et al 1966). It is in this context that one must view with some scepticism the claims that some immediate anurias are hyperacute rejections in the sense that HLA-sensitization had occurred before the transplant.

By formal experimentation, one can arrange a series of second-set rejections so as to provide some data concerning the functional, hemodynamic, microscopical and immunological aspects of such reactions. From such experiments it can be established that the tempo and the intensity of the reaction varies and that, in a percentage of subjects which appear to have been adequately sensitized, no second-set reaction occurs at all (Pinco et al 1970). It has also been established that the earliest arteriographic evidence capable of explaining the sudden onset of oliguria or anuria involves outer cortical exclusion from perfusion (Pineo et al 1970; Dempster 1971a). Rather than a generalized vasoconstriction of the whole arterial tree, as previously suggested (Dempster 1953a), the earliest damage would appear to be in the afferent arterioles and glomeruli of the outer cortex, general afferent vasoconstriction follows later. Previous arteriographic assessments of the nature of second-set rejections were made at 12 or 24 hours after transplantation; in most cases this would be many hours after the onset of anuria (Dempster 1953a). Arteriography at this late stage demonstrated generalized vasoconstriction and the in-

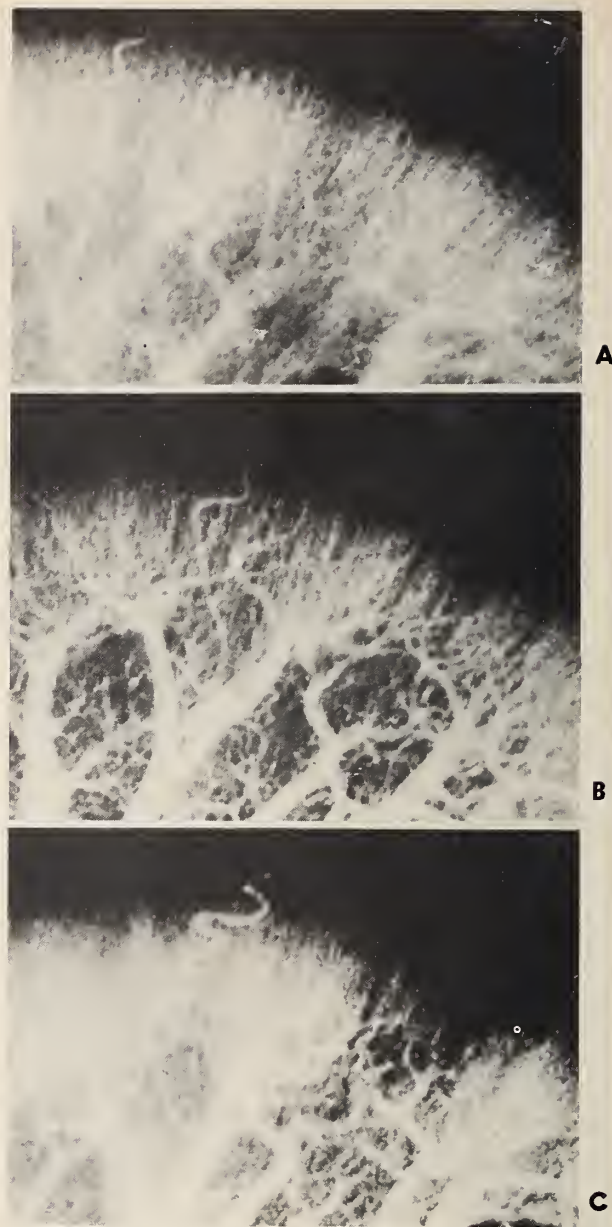


Figure 7.—Successive arteriograms over a period of six hours in a second-set kidney transplant rejection. (a) Immediate post-transplant oliguria. (b) Two hours later anuria has occurred. (c) Two hours later the anuric state continues and now the renal blood flow is reduced markedly. (Pineo G F, Regoeczi E and Dempster W J, 1970): *Brit J Exp Path* 51:547-562, 1970).

terpretation was that anti-kidney antibodies were mopped up by the vascular endothelium generally, so leading to a state of generalized vasoconstriction due to a supersaturation by anti-kidney antibodies.

Recent experiments (Pineo et al 1970) have indicated that the first sign of the second-set re-

action is inadequate perfusion of the outer cortex and this is associated with severe oliguria or anuria (Figure 7). The generalized vasoconstriction which is evident in second-set kidneys left in situ for 12 to 24 hours after the onset of anuria or oliguria might reasonably be explained by increased renal peripheral vascular resistance. To this should be added vascular damage resulting in areas of fibrinoid necrosis which probably induces some degree of vasoconstriction (Dempster 1953a). It would appear, therefore, that anti-kidney antibodies are first deposited on the glomerular basement membrane and only later in the rest of the renal afferent vessels. This can be explained by the classical reasons of increased hydrostatic pressure and tenuous endothelium in the glomerular capillaries. Since previous grafting with skin can evoke antibodies against the coronary vessels and so produce a second-set heart transplant reaction (Dempster 1968), it is not to be expected that this type of antibody would be exclusively anti-glomerular basement membrane. This is supporting evidence that several tissues contain common antigens in their capillary systems (Krakower and Greenspon 1958). One must look more closely at the glomeruli and afferent arterioles in order to understand the earliest changes since it is likely that damage occurs simultaneously in glomeruli and afferent arterioles.

Now that the significance of the HL-A cytotoxins in relation to hyperacute rejection is so equivocal and contradictory (Stewart et al 1969; Patel and Terasaki 1969), little is to be gained by taking up entrenched positions and attempting to explain exceptions to the poorly established rule as false negatives or false positives (Heale et al 1969; Morris et al 1969). Turcotte et al (1970) have described several cases of immediate post-transplant oliguria or anuria. There was poor function in 21 out of 29 cases, which is an extraordinarily high incidence and especially since the donors were live and related. Of these, two were positive HL-A cross matches but both recovered function subsequently. Poor function in the immediate post-transplant phase was attributed, by these observers, to hypovolemia and to an antibiotic, cephalothin—that is, technical factors. The evidence with respect to cephalodine as a nephrotoxic agent is equivocal and a more likely cause is the “flush out” solution. These investigators might have looked again at the flush out

used—Ringer-lactate solution, which can also disturb renal hemodynamics after transplantation. The recipients were not hydrated, which also can lead to post-transplant oliguria or anuria. So little was the concern for the number of blood transfusions and pregnancies that no information is provided by the investigators, but there would appear to be more males than females involved in this high series of post-transplant oliguria. Whether kidney transplant recipients are positive or negative for HL-A antibodies is irrelevant clinically. These antibodies are irrelevant experimentally since injected lymphocytes (by subcutaneous, intraperitoneal or intravenously) do not sensitize a recipient to a kidney or a heart subsequently transplanted (Calne et al 1966; Dempster 1969a). Some correlation between antigens of leukocytes and skin were reported by Medawar (1946) but I have never been able to confirm this in dogs, and the data on humans are not convincing. The debate as to whether pregnancy or blood transfusions are responsible for these hyperacute rejections is based on evidence so tenuous and contradictory that it can hardly be taken seriously. Pregnancy and blood transfusions were in the background from the beginning of kidney transplantation, so what has happened in recent years to bring about the recent spate of reports about hyperacute rejection caused by previous sensitization?

From a period when no one seemed to be experiencing any immediate post-transplant anurias we are now in a phase when it has become, or perhaps was, a major pre-occupation of most clinical units. Partly, this is due to the fact that second kidneys are being transplanted more frequently in the last three years than previously. Early post-transplant anuria, in a proportion of these second kidneys, is undoubtedly due to pre-existing anti-kidney antibodies developed against the rejected first kidney and some degree of cross-sensitization can account for this (Williams et al 1969). Partly, the universal use of cadaveric kidneys has led to a high incidence of post-transplant anuria from which many recover normal or adequate renal function. Since Najarian et al (1966) were courageous enough to admit frankly to several cases of immediate post-transplant anuria due to inadequate hydration and most probably hypovolemia which is a known cause of renal vasoconstriction (that is, technical rather than immunological causes), a climate has been

created wherein post-transplant anuria can be discussed without loss of face. Turcotte et al (1970) have recently admitted to immediate satisfactory function in only eight out of 29 human allotransplants.

The history of immediate post-transplant anuria is similar to that of "dumping" after gastrectomy: at first, few would acknowledge the reality of this complication while later anyone not encountering this and other complications after gastrectomy could not be regarded as serious gastroenterologists. A classification consisting of four different types of post-transplant anuria (Dempster 1954, 1963) was generally regarded, even a few years ago, as rather bizarre. For instance, Hamburger et al (1964) commented, with a touch of ridicule, "It is also possible that Dempster has observed the same phenomena, but this author seems to encounter so many more anuric complications than the other groups, even in autotransplantation, that the interpretation of his findings is not easy." What Hamburger et al (1964) failed to appreciate was that Type 4 anuria was deliberately produced by the second-set reaction, requiring to be set apart from Type 3, the usual first-set rejection anuria, and Types 1 and 2, immediate post-transplant anurias occurring in autotransplants as well as in first-set allotransplants. It is Type 4 anuria due to a second-set type of rejection, which has now become an important clinical problem. Indeed, Hamburger et al (1962), without producing any objective evidence, claimed that preexisting antibodies were responsible for two of their three cases of immediate post-transplant anuria; this is equivalent to suggesting that a second-set rejection was responsible (that is, anuria in a previously sensitized animal); such a reaction is classifiable as a Type 4 anuria. In their report on immediate post-transplant anuria in live first-set kidneys a figure of 50 percent was given, a rather high figure.

Kissmeyer-Nielsen et al (1966) in their report of hyperacute rejection seemed unaware of the literature on second-set kidney rejection since they could find no parallel to their own two cases of immediate post-transplant anuria other than the "white skin graft." The second-set kidney rejection is a phenomenon which has to be measured in minutes or hours whereas the "white skin graft" can be either a technical failure or not and requires a few days to develop. Other clinical

groups have also failed to establish experimentally the necessary criteria for assessing second-set kidney rejection (Williams et al 1969; Starzl et al 1968).

In the discussion of the paper by Najarian et al (1966), Hume reiterated his view that with adequate hydration one should never encounter immediate post-transplant anuria in first-set kidneys and, if one does, the cause is probably technical due to hypovolemia in humans or hemoconcentration in dogs. With this view I am essentially in agreement. The data missing from Hume and Egdahl (1955), however, is the incidence of post-transplant anuria without adequate hydration, which must surely have provided the incentive to hydrate the animals before transplantation. It is interesting that the latest figures from Hume's group (Williams et al 1969) admit that four out of five first-set transplants failed to function and that in three out of these four the failure could fairly be claimed to be due to technical causes.

In a review of the growing problems of clinical renal transplantation, Dempster and Kountz (1966) drew attention to the probable complications of transplanting a second kidney from a different donor in man; the danger being, in a significant proportion, of cross-sensitization precipitating a second-set rejection which would present as immediate post-transplant anuria. Hume et al (1966) challenged this warning rather prematurely: "The results of second kidney transplants in man to date, however, do not seem to bear out either of these contentions." Yet, three years later there was a change of emphasis: "During the past two and a half years, ten of sixteen secondary renal allografts performed at the Medical College of Virginia did not function. This experience has been disconcerting since 11 of the secondary grafts carried out prior to 1967 functioned." The above data highlight the way medical experience develops and emphasizes the limitations of publishing insufficient data too soon. Stated another way, over a period of four years, 27 second kidney transplants were performed; of these, ten failed to function, which gives a cross-sensitization figure of 37 percent. This corresponds to the predicted data in humans as derived from skin grafting (Rapaport et al 1962) and from canine kidneys (Dempster 1953a). It is probable that a range of 30 to 45 percent may be a reasonable forecast although the figures reported by Naka-

moto et al (1967) are surprisingly high. The only means, at present, of finding out whether a second transplant will be rejected immediately is to transplant and await events. Alternatively, it would be essential to lymphocyte type and attempt to correlate second-set rejection due to an overlap of lymphocyte antigenic factors. But lymphocyte typing is so unreliable that this will probably be a fruitless task. It is this series of post-transplant anurias (Type 4—Dempster 1954, 1963, 1969a) which can be regarded, until proved otherwise, as second-set rejections due to cross-sensitization or to a wide spectrum of antibodies being evoked by the rejection of the first kidney.

The real debate concerns the significance of immediate post-transplant anuria in first-set kidneys and the validity of incriminating, as sensitizing agents, antibodies evoked by pregnancy or blood transfusions or both. Patel and Terasaki (1969) reported that in 14 percent of 157 first-set transplants in females and 6.3 percent of 256 first-set transplants in males there was immediate post-transplant anuria. This would suggest that this complication is more frequent in females and since both sexes are dialysed or are blood-transfused before transplantation the discrepancy can be explained more easily by pregnancy cytotoxins. However, it is evident from the data so far that parous females are no more liable than males to immediate post-transplant anuria.

There is considerable dispute concerning the relationship between pre-existing cytotoxins due to blood transfusions or pregnancy and immediate post-transplant anuria. Terasaki et al (1967) reported that a woman had immediately rejected a kidney from her husband by whom she previously had borne two healthy children. Without any details of the cross-match test it was assumed that the cause of this immediate post-transplant anuria was pregnancy antibodies.

It should be appreciated that pregnancy leucoagglutinins are complete antibodies whereas antibodies derived from multiple blood transfusions are usually incomplete (Engelfriet and van Logham 1961). Thus, two different types of antibody and sometimes a combination of the two are supposedly involved in hyperacute rejection. If leucocytotoxins are identified then, again, they are entities different to leucoagglutinins. Furthermore, more than three pregnancies are required to raise the leucoagglutinin titre to detectable levels (van Rood et al 1959); the num-

ber of blood transfusions required is not yet agreed upon but no effect has been encountered after over a hundred.

There is no evidence that HL-A antigens cross-react with glomerular basement membrane (Dixon 1969) which is the target in second-set reactions in kidney allotransplants (Dempster 1953a) and in long surviving human first-set kidneys after reversal of early rejection episodes. Is there any evidence that HL-A antigens cross-react with vascular endothelial cells?

The conflicting views regarding pregnancy as a period of immunological inertia (Anderson 1965) or intense immunological activity (Terasaki et al 1967) are clearly not reconcilable at present. This conflict is reflected in contradictory reports and views. If a fetus evokes no more maternal reaction than the production of low titre leucocyte antibodies one need not regard pregnancy as a period of intense immunological activity, especially since several pregnancies are required to evoke a detectable titre. As with Rh sensitization, only when the maternal circulation is invaded does sensitization occur. Antigen administered intravenously is not generally regarded as effective. This attitude is derived from experiments conducted by Medawar (1946) in which leucocytes injected intravenously did not sensitize whereas they did when injected intradermally. This concept is of no practical validity since allotransplanted organs can very effectively sensitize via the intravenous route. The view of Terasaki et al (1967) quoted above is in strange contrast to that of Ceppellini et al (1966) who reported "... the two grafts with the longest survival were observed in a recipient woman who had ended her pregnancy three months before grafting." This implies, for some unknown reason, a connection between pregnancy and the length of survival of skin grafts. Granted that leucoagglutinins are developed during pregnancy, should this form of sensitization endure for all time when it is, theoretically, no different from sensitization by a skin graft? Rapaport and Converse (1958) reported that sensitization by a skin graft may disappear by 80 days in spite of the fact that a skin graft is widely considered to be the most potent transplantation sensitizing agent.

The conclusion drawn by Terasaki et al (1967) is rather undermined by the surprising data of Goodman and Masaites (1967) which shows

that, in a study of 1553 women, the incidence of pregnancy antibodies is less after the second pregnancy than after the first. Thus, women are at less risk after the second pregnancy—if, indeed, there is any risk at all engendered by these antibodies. Serum which reveals cytotoxicity *in vitro* may not be toxic *in vivo*, and this difference has still to be evaluated. What credence can be given to the claims that pregnancy antibodies cause immediate second-set rejection of a first-set kidney allotransplant when these same antibodies cause no damage to fetal leucocytes against half (that is, the male contribution) the antigens of which they were developed in the first place?

Ever since Ehrlich discovered antibodies in the serum of pregnant women various speculations as to the diseases they may cause have ranged from toxemia of pregnancy to fetal abnormalities. Recent analyses refute any connection between pregnancy cytotoxins and fetal abnormalities or neonatal leucopenia (Berah et al 1966). These investigators even dispute the report of Jensen (1962) that the antibodies are more frequently developed in premature babies; their data support the opposite view. Halbrecht and Komlos (1968), in a rather small series, return to the theme that pregnancy abnormalities are due to HL-A incompatibility. Their testing was done with the mixed lymphocyte (husband-wife) test; with two normal pregnancies there was good matching, but at the other end of the scale hydatidiform mole was associated with an increased number in transforms. Since there would appear to be no correlation between the lymphocyte transform test and HL-A leucocytotoxicity tests (Debray-Sachs 1968) one is in no position to draw any definite conclusions.

Correlations with Length of Survival

There are many facets to rejection (Table 4) so that to try to correlate lymphocyte typing alone with length of survival is unrealistic. It is seldom possible to control immuno-suppression rigidly in a whole series of cases because of clinical complications. All these aspects must be assessed before one may come to any conclusions about histocompatibility factors and length of survival.

A distinction should be drawn between lymphocyte typing which is now progressing satisfactorily and the actual histocompatibility rela-

tionship to other tissues. Just because the HL-A system is a genetic antigenic polymorphism does not automatically link it to tissue histocompatibility any more than other such polymorphisms—serum β -lipoproteins, haptoglobins, serum cholinesterase and the like. Although there appears to be common antigens to skin and heart and kidney, there is little evidence to convince one that lymphocytes can sensitize a recipient to a subsequently transplanted kidney or heart. In fact, the standard method of sensitizing is now by skin grafting (Dempster 1953c) since lymphocytes have proved useless in the larger mammals (Calne et al 1966; Simpson et al 1970). Having encountered this problem with lymphocytes, the author was provided with the incentive to seek other tissues, like skin, with antigens in common with kidney. But even when a highly successful tissue such as skin is used to presensitize, a few instances of failure to evoke a second-set reaction in allotransplanted kidneys have been reported (Pineo et al 1970; Najarian 1970). Sometimes, also, the Shwartzman reaction itself fails to occur after the second challenge of endotoxin.

Considering that virtually nothing is known about the mechanism of lymphocytotoxicity against grafts *in vivo* or the strengths of the HL-A antigens *in vivo* or whether any one is of critical importance for rejection *in vivo* and the fact that HL-A antibodies *in vivo* have not even yet been categorized with respect to (1) their degree of affinity, (2) their ability to fix complement *in vivo*, (3) their cytotoxic role if not complement-fixed *in vivo*, (4) the site of union of antigen and antibody *in vivo* and its sequelae as well as the recognized necessity of using skin rather than lymphocytes to presensitize experimentally against organ transplants—considering those points it was by an extraordinary *tour de force* of mass persuasion that claims were pushed for HL-A antigens as precise markers of exact degrees of histocompatibility with respect to transplant survival. If, even now, no convincing correlation has been found between graft survival and 25 HL-A antigens (including the commonest and the allegedly strongest) it is unlikely that a correlation will be established by discovering more rare antigens.

The characteristics of the second-set kidney transplant reaction (hyperacute rejection—when genuine) can now be set down:

TABLE 4.—Possible Correlations in Tissue Matching

Successive Kidneys	TISSUE MATCHING		Pre-existing } Blood transfusion Cytotoxins } Pregnancy
	1. Varying sera 2. Increasing antigen detection 3. Varying criteria of matching and mismatching		
Genetic Relationship	First-set Kidneys		Skin Antigens
	RENAL FUNCTION		
Basement Membrane Antigens	Good match — good function?	TISSUE DAMAGE	REJECTION EPISODES IN EARLY STAGES
	Mismatch — poor function?	Frequently more severe than the clinical state betrays.	
	REJECTION EPISODES IN LATE STAGES		Severe } Moderate } Stage at which Mild } detected and treated.
	SURVIVAL		
	Severe } Moderate } Mild }	Good match ? less rejection	STATE OF DONOR KIDNEY
	STEROID TOLERANCE AND DIFFERENCES IN REACTIVITY		
	1. Tolerance of large doses in early stage	good poor	1. Age of donor 2. Degree of ischemic damage: anuric 10 days } less more 3. Pre-existing disease, e.g. pyelonephritis.
	2. Utilization of large dose in early rejection	good poor	
	3. Tolerance of maintenance doses and utilization	good poor	
	4. Tolerance of prolonged high steroid dosage	good poor	
	5. Presence of complications requiring reduction or withdrawal of steroid	Yes No	

• Adequate presensitization is not invariably followed by a second-set reaction (Pineo et al 1970; Najarian 1970).

• It is not dependent on complement fixation *in vivo* (Dempster and Brown 1971).

• It is not abrogated or reduced in severity by rendering incoagulable the blood of recipients (Pineo et al 1970).

• Systemic intravascular coagulation is not the primary factor (Pineo et al 1970).

• Renal vasoconstriction, especially of the outer cortical vessels, is the first sign of the reaction (Dempster 1953a; Pineo et al 1970; Dempster 1971).

• Once started, the reaction proceeds inexorably to profound irreversible parenchymal damage with fibrin deposition in the glomeruli and afferent arterioles (Dempster 1953a; Pineo et al 1970; Dempster 1971b).

• Polymorphonuclear cells are not consistently sequestered in the capillaries of the damaged glomeruli (Dempster 1953a; Pineo et al 1970; Dempster 1971). Such cells may be observed in autotransplants following a hemodynamic upset and hence cannot be the effectors of allogenic or xenogenic rejection (Dempster 1953b).

• The renal vascular basement membrane bears the brunt of the reaction (Dempster 1969 a; Pineo et al 1970). Basement membrane antigens are not represented on lymphocytes so that it is quite improbable that HL-A antibodies are involved since they are complement fixing—*in vitro*, at least. This is the most important single factor against a hypothesis that lymphocytes act as significant histocompatibility markers.

On this evidence, it is even difficult to fit the second-set kidney transplant reaction into any class of renal antigen-antibody reactions. In

acute glomerulonephritis, for example, there may be renal hyperemia and a concentrated urine may be produced—the exact antithesis of the second-set reaction. There is, on the other hand, a certain similarity (but no more than that) to the Shwartzman reaction (Dempster and Brown 1971) and to a very severe Masugi nephritis (Shigematsu 1970). The second-set kidney transplant reaction is independent of complement fixation *in vivo* whereas all the current indicator systems and reports (Kissmeyer-Nielsen et al 1966) of cross-reactivity of serum with kidney homogenates involve complement fixing antibodies—*in vitro*. Further, the actual site of union of antigen and antibody and its cytopathology were not established, which is crucial because cross-reactivity is no proof of cytotoxicity. The ultimate test of histocompatibility is not derived from an *in vitro* test, but from the actual *in vivo* behavior of the recipient. Claims (Starzl et al 1970) of second-set rejection by HL-A antibodies not even detectable in the serum cannot be discussed seriously.

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INFECTION FROM BRONCHODILATOR SPRAYS

A troublesome complication in patients with chronic respiratory insufficiency is the transmission of infection by various bronchodilator aerosol devices. . . . The most common organism sprayed into the hospitalized patient is *pseudomonas*. It's very difficult to eradicate; it occurs in the large bulk nebulizers, particularly the heated devices; and it requires a meticulous program of sterilization and cleansing of the equipment and daily changing. You just can't reuse any part of the machine or apparatus which has been exposed to the expired air from another patient.

Home management of the various inhalation therapy devices is somewhat easier because the patient is not exposed to the hospital organisms. But the possibility of infection still must be considered. You can't just give a patient a machine and tell him to wash it out once in a while. He's got to have a good program where he washes the unit and all the exposable parts with soap or perhaps a detergent. A useful system, if the patient has a nebulizer powered by a compressor, is to have him aerosolize 0.25 percent acetic acid or about 6 cc of white vinegar into a pint of water every couple days for about 10 minutes.

—PHILIP KIMBEL, M.D., Philadelphia
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Evaluation of Renal Vascular Hypertension And Primary Hyperaldosteronism

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. EARLEY:* We are fortunate to have Dr. Edward Biglieri with us today to discuss the various aspects in the diagnosis and treatment of hypertensive states associated with an excess of mineralocorticoid hormone.

DR. BIGLIERI:† The work-up of the hypertensive patient has, in essence, become the search for the "nonessential" hypertensive patient. We now have at hand the capabilities of measuring many critical substances, particularly aldosterone and renin, that provide the information that may lead to a cure of the hypertension or provide valuable prognostic information. The indications for these measurements and the problems in interpretation are the main substance of this discussion.

The incidence of curable, or correctable, hypertension in the 10 to 15 percent of the population who have hypertension varies greatly. Of all cases of hypertension, the figures for primary aldosteronism range from 0.5 to 6.7 percent and for renovascular hypertensive disease from 3 to approximately 20 percent in certain series (or more realistically 5 percent). Today we shall discuss various aspects of hypertension associated with primary hyperaldosteronism and renovascular hypertension.

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Primary Hyperaldosteronism

*Features in the Clinical History*¹⁻³

Even though primary aldosteronism is probably a moderately rare disease, it seems to be a very common one in our geographical area. For the first time in many years, we have had eight patients with this disease in the Clinical Research Center at the same time, a fact which indicates increasing recognition of primary aldosteronism. Unlike cortisol-excess, aldosterone excess has no clinical stigmata. Headaches are very common in patients with primary aldosteronism and are almost immediately relieved postoperatively. Most of the symptoms are related to potassium depletion: fatigue, weakness, polyuria, and nocturia. Demonstration of transient hypertension during pregnancy is an important point in the history and is invariably present in female patients with an aldosterone-producing adenoma (APA). Transient hypertension during pregnancy may also be common in patients with incipient renovascular hypertensive disorders. Young patients, particularly children, with sudden onset of hypertension must be carefully screened for correctable causes of hypertension. Numbness and tingling of the extremities are frequently associated with the hypokalemic alkalosis. It is important to note whether or not patients have been taking any

TABLE 1.—Diagnostic Decision Diagram*

			Aldosterone level after	
			PRA	DOCA
Hypertension ↓ Hypokalemia ↓ Aldosterone Level →	Elevated	Primary adrenal causes		
		1) Aldosterone-producing adenoma	↓	→
		2) Idiopathic hyperaldosteronism	↓	→
		3) Glucocorticoid-responsive	↓	→
		Secondary adrenal causes		
		1) Malignant hypertension	↑	↓
	Normal	2) Renovascular hypertension	N or ↑	↓
		3) Estrogens and essential hypertension	↑	↓
		4) Diuretics and hypertension	↑	↓
	Reduced	Other MCH (Correction of hypokalemia would suggest another MCH)	↓	
		1) 17-hydroxylation deficiency (DOC excess)	↓	
		2) 11-hydroxylation deficiency (aldosterone N or ↓)	N or ↓	
		3) Primary DOC lesion	↓	

*↑=increased, ↓=reduced, →=no change, N=normal, PRA=plasma renin activity, DOCA=change in aldosterone production after DOCA administration, MCH=mineralocorticoid hormones, DOC=deoxycorticosterone.

kind of steroid, diuretic, licorice, or, most important, oral contraceptive. It is also important to estimate dietary sodium and potassium intake because moderate salt restriction can correct the hypokalemia and many of the metabolic abnormalities of aldosteronism. In general, patients with severe hypertension due to an APA respond poorly to antihypertensive therapy, even if vigorously applied. If antihypertensive therapy effectively reduces blood pressure and serum potassium levels are restored to normal, it is unlikely that the patient has primary aldosteronism. But if hypokalemia persists, the pursuit of the diagnosis should be intensified. A metallic taste is frequently reported by patients with severe potassium depletion. This peculiar sensation disappears when potassium defects are corrected.

Salient Features on Physical Examination

The most important observation on physical examination is the consistent demonstration of hypertension, which can range from very mild and labile to very severe and persistent. While malignant hypertension is rare, it has occurred in patients with primary aldosteronism. When potassium depletion is severe, postural falls in blood pressure are easily noted, but not associated with

compensatory tachycardia. In association with severe potassium depletion, an abnormal response to the Valsalva maneuver may be present, with an absence of hypertensive overshoot and bradycardia. Chvostek's or Trousseau's signs, or both, in the untreated hypertensive patient again strongly suggests the possibility of hyperaldosteronism. In the 94 patients with an APA whom we studied, the only consistent fundoscopic findings were increased A-V nicking and an increase in the venous:arterial ratio. While cardiomegaly was frequently present, it was not a consistent finding. The absence of an abdominal bruit was an important observation. It is, however, important to bear in mind that a bruit may not be heard in at least 25 percent of patients with renovascular hypertension, while as many as 20 percent of patients without renovascular hypertension may have a bruit.⁴

Laboratory and Clinical Studies

For Outpatient Screening

Potassium concentration measurement. The most important screening procedure for hyperaldosteronism is the measurement of serum potassium concentration (Table 1). We prescribe 2 grams of sodium chloride with each meal for

four days before measuring Na, K, Cl, and CO₂ concentrations and hematocrit. During this time changes in the electrocardiogram should be followed since potassium depletion is intensified by this maneuver in the patient with primary aldosteronism. If either unprovoked hypokalemia or provoked hypokalemia is demonstrated on more than one occasion, the measurement of aldosterone is indicated. Patients receiving diuretic therapy do cause problems, and a useful rapid screening technique to determine whether diuretics are the cause of the hypokalemia is to measure the excretion of potassium in the 24 hours immediately following discontinuance of diuretic therapy. Frequently the urinary potassium level ranges from less than 20 to as much as 30 mEq per 24 hours, which indicates intense potassium conservation. Excretion of more than 50 mEq potassium per 24 hours with hypokalemia is again presumptive evidence of aldosterone excess.

Aldosterone measurement. Outpatient aldosterone measurements are fraught with difficulties.⁵ The abnormal elevations which are not due to primary hyperaldosteronism usually result from (1) the outpatient's failure to observe the precollection requirement of increased salt intake, (2) the great variation in day-to-day aldosterone production in the hypertensive outpatient, (3) the sensitivity of aldosterone production to stress, trauma and discharges of adrenocorticotrophic hormone, and (4) the influence of drug therapy, particularly diuretics and estrogen (estrogen compounds usually elevate aldosterone production).⁶ If sodium excretion is less than 50 mEq per 24 hours, aldosterone is not measured.

Of 150 hypertensive outpatients admitted to the Clinical Study Center because of demonstrated hypertension and reduced serum potassium concentrations, only 25 still had high urinary aldosterone values. In a controlled environment with fixed sodium intake, aldosterone production is normal in patients with essential hypertension. Further studies of the 25 patients in the hospital showed suppression of aldosterone excretion after administration of deoxycorticosterone acetate (DOCA), persistently normal serum potassium levels, and mostly normal levels of plasma renin activity (PRA). Several patients had borderline to low renin levels during sodium restriction. In the presence of aldosterone suppression, low

renin levels either represented an early phase of primary aldosteronism or an as yet nondiagnosable hypertensive disorder. We have followed some of these suspects for several years and the patterns have persisted. Whether or not these patients have an incipient APA is not clear at this time.

Control of the great variability in outpatient aldosterone measurements is attempted in several ways. Ingestion of a large quantity of salt has proved useful at times, but is poorly tolerated by the patients. Our approach is to prescribe a liberal salt intake (more than 6 grams per day) and 9 α -fluorohydrocortisone (Florinef®), 100 μ g in divided doses given orally four times a day for three consecutive days.⁷ The urinary specimen is collected on the third day. This serves as a mild DOCA suppression test in outpatients, although it is not quite as reliable because of the lower level of mineralocorticoid administered. Aldosterone levels in patients with secondary hyperaldosteronism will suppress into the normal range. If, however, the level of aldosterone in such a specimen is elevated, we believe the patient should be put into hospital for more definitive testing, such as administration of large amounts of DOCA (10 mg every 12 hours for three days) and measurement of plasma renin activity. Plasma renin activity is difficult to measure in the outpatient because diet and posture must be carefully controlled.

Definitive Laboratory and Clinical Inpatient Studies (Table 1)

Potassium concentration measurement. The approach to the investigation of a hypertensive patient for a hypermineralocorticoid state in the hospital is as follows. All hypertensive patients should have several serum potassium concentrations measured after oral salt loading. Only after the repeated demonstration of hypokalemia should the scheme outlined herein be followed. If serum potassium is consistently normal, I believe that no further investigation for primary aldosteronism should be pursued, but that the preliminary diagnosis should not be forgotten. The patient should be reexamined periodically if there is any suggestion that aldosterone excess may occur.

Plasma renin activity (PRA) measurement. As our knowledge of the renin-angiotensin system increases, the conditions under which PRA are

measured are most crucial. Plasma renin activity is not measured in a patient who walks into the office. Meticulous attention should be given to diet and posture. The measurement of PRA is becoming increasingly important in confirming the presence or absence of primary hyperaldosteronism. The most frequently used method of measuring PRA is obtaining the blood specimens during the stress of sodium restriction and four hours of the upright or sitting posture.⁸⁻¹¹ This technique may not be the most definitive. These maneuvers are potent stimuli to the renin-angiotensin system and may cause a subnormal renin level to increase to normal. The most discriminating measurement of the renin-angiotensin system in primary aldosteronism is the measurement of basal plasma renin concentration (PRC) after overnight recumbency. Least variance occurs when renin is measured under these circumstances.¹²

Aldosterone measurement. Elevated levels of urinary aldosterone in a hypokalemic hypertensive inpatient are further presumptive evidence of primary aldosteronism due to an APA, although the possibility of secondary hyperaldosteronism must still be considered. Secondary hyperaldosteronism in hypertensive patients (that is, malignant hypertension, renovascular hypertension, and essential hypertension due to estrogen or diuretic therapy) is usually easily identified by either history or physical examination. However, two additional measurements are most helpful in distinguishing between primary and secondary hyperaldosteronism: the measurement of PRA or PRC and the measurement of aldosterone after administration of 10 mg of DOCA intramuscularly every 12 hours for three days. Primary adrenal oversecretion of aldosterone results in hypertension and hypervolemia, which suppress renin production, as measured by PRC and PRA. In patients with secondary hyperaldosteronism, PRA or PRC levels are elevated due to probable intrarenal nephrosclerosis and vasospasm in malignant hypertension, decreased renal arterial pressure in renovascular hypertension, increased renin substrate and activity but not concentration in estrogen-treated patients, and reduced circulating blood volume after diuretic treatment. The administration of DOCA as described helps establish autonomy and a functioning renin-angiotensin system.¹³ The already high levels of aldosterone in patients with an APA are never reduced into

the normal range by DOCA. However, suppression of the elevated levels into the normal range occurs after DOCA in patients with secondary hyperaldosteronism.

There are at least three primary adrenal causes of primary aldosteronism: (1) an APA, (2) idiopathic hyperaldosteronism (IHA), pseudo-primary aldosteronism¹⁴ or nodular hyperplasia, and (3) glucocorticoid-remediable hyperaldosteronism.¹⁵ Glucocorticoid-remediable hyperaldosteronism which is rare, is readily apparent if treatment with 1 mg of dexamethasone for one week corrects the hypertension and hormonal abnormalities. (This observation makes a strong point for the existence of still another aldosterone-stimulating agent.) The distinction between an APA and IHA is most difficult. Patients with IHA are more than likely male, the mean serum potassium concentration is subnormal (but not as low as in patients with an APA), and urinary aldosterone levels are not as elevated as in patients with an APA. Levels of PRA are less reduced in patients with IHA than in those with an APA. The distinction between the two is of great importance because the removal of nodular hyperplastic glands usually does not result in cure or amelioration of hypertension, although potassium depletion and its effects are corrected. The measurement of PRC after overnight recumbency during a normal salt intake (more than 120 mEq per day) seems to be the most useful discriminating procedure: the levels are usually less than 1 nanogram per ml in patients with an APA and between 1 and 3 nanograms per ml in patients with IHA (normal range is 3 to 9 nanograms per ml).¹² Adrenal venography and bilateral catheterization of the adrenal veins for measurement of aldosterone concentrations may be helpful, but are not entirely successful even in specialized units.

Normal levels of aldosterone in the hypertensive hypokalemic patient do not necessarily exclude the diagnosis of primary aldosteronism. Adrenal production of aldosterone may reach the normal range in a patient with an APA who is severely depleted of potassium. Potassium repletion effects a great increase in the urinary aldosterone level. A patient with essential hypertension whose physical activity and salt intake are well controlled rarely has increased aldosterone production. However, it is important to note that one-fourth to one-third of the patients with essential hypertension have subnormal renin val-

ues. The cause is not known, but some of them may harbor a subclinical APA.¹⁶⁻¹⁸

Other steroid measurements. Subnormal urinary aldosterone levels in a hypokalemic hypertensive patient should immediately suggest the possibility of the overproduction of another mineralocorticoid hormone, especially if PRA is also reduced. Further evidence can be obtained by administration of spironolactone, 200 to 400 mg per day for several weeks. Correction of the hypokalemia and high blood pressure could be further evidence that deoxycorticosterone (DOC) secretion is increased or, if not DOC, possibly an unrecognized mineralocorticoid hormone. These findings are seen in patients with the 17-hydroxylation syndrome.¹⁹ In these patients, who are usually hypogonadal females with primary amenorrhea or male pseudohermaphrodites, aldosterone and 17-hydroxysteroid levels are low, but corticosterone and deoxycorticosterone levels are elevated.

Renovascular Hypertension

Screening Procedures

What assessment should be made of the hypertension in the hypertensive patient with renovascular lesions? It is important to review, if somewhat briefly, some of the more important facts of renovascular hypertensive disorders. In our review of the efficacy of the many diagnostic screening tests available, only reports of patients whose hypertension was cured by removal of a stenotic lesion can be accepted, although the frequency of functionally insignificant renovascular disease is much higher. Renovascular disease is not uncommon, and in various reports some degree of stenosis was demonstrated arteriographically in up to 32 percent of normotensive patients and in up to 67 percent of hypertensive patients.²⁰ The postmortem finding of renovascular stenosis in a large unselected population is a frequent finding (approximately 50 percent).²¹ Anomalies of the renal arteries may be present in approximately two-thirds of hypertensive patients; functional significance of these anomalies is unknown.²²

Establishing the functional significance of these lesions is essential before making the therapeutic decision. As mentioned earlier, the frequency of renovascular hypertension is quite variable. For example, it is much lower in the Negro hypertensive population and much higher in diabetics.

Some of the clinical features pointed out earlier should be reemphasized.

As many as 25 percent of patients with renovascular hypertension may not have an abdominal bruit, and as many as 20 percent of patients without renovascular disease may have an abdominal bruit. In general, fibromuscular dysplasia is the usual cause of hypertension in patients under 30 years of age, and arteriosclerotic renovascular lesions are the common cause in patients over 50 years of age. Secondary aldosteronism again is an occasional observation and, in our particular experience, probably represents an early phase of significant renal arterial narrowing.²³ Nephrotic syndrome has been described in three patients with renal artery stenosis and sometimes in patients with polycythemia.

In every hypertensive patient renovascular hypertension must be ruled out. The diagnosis is best approached by multiple probing using several of the many tests available, rather than relying on a single test.

Intravenous pyelogram. The rapid-sequence intravenous pyelogram is certainly the most useful screening test to employ first in the evaluation of a hypertensive patient because of its availability, safety, ease of performance, and interpretation. The criteria used in determining a lesion in the pyelogram may vary considerably, but certainly a difference in renal length, a delay in appearance of dye or hypoconcentration of dye in the early films and hyperconcentration on one side in late films, abnormalities in the silhouettes of the nephrogram, and ureteral notching are all helpful. Most of these abnormalities are found in some degree in approximately two-thirds of the patients with renovascular hypertension. In 15 percent of cases, however, renal artery stenosis may be present although the intravenous pyelogram is normal. Moreover, 10 percent of patients with these abnormalities on intravenous pyelogram may have renal parenchymal disease rather than a renal artery stenosis.

Renogram. Another radiological procedure used less frequently because of its somewhat limited value, except in specialized units, is the radioisotope renogram. Our experience with the radioisotope renogram is relatively limited, as we use it only rarely in evaluating hypertensive patients. Interpretation of the renograms is difficult, although the procedure is safe and easy to perform.

Definitive Studies

Renal split function studies. Bilateral ureteral catheterization studies use an excretory function of the kidney to assess a probable hormonal defect. Decreased urine volume and sodium concentration and increased pH and concentrations of nonabsorbed solutes, creatinine, and inulin indicate ischemic abnormalities. Certainly a positive result is most informative, but it primarily indicates only the presence of major renal arterial disease and is of limited value in identifying bilateral or segmental lesions and is not always predictive of a surgical cure. The validity of the test depends on the medical team who perform it.

Renal arteriography. Once an abnormality is detected, particularly by the intravenous pyelogram, it is the general practice in this community to employ renal arteriography to identify the abnormality further. There are many questions that are raised by arteriography that still remain unanswered, particularly the functional significance of a lesion. Although radiographical techniques with intensification of smaller lesions have improved tremendously and enable careful examination of segmental lesions, we still do not know the significance of many of the abnormalities, such as multiple renal arteries. We often do not know the meaning of embolic episodes or infarction in the kidney. In view of the high incidence of renal artery constriction in both hypertensive and nonhypertensive patients, it becomes important to demonstrate whether or not the lesion is of functional significance and is producing substances that may be involved in the hypertensive process.

Plasma renin activity measurement. Measurement of plasma renin activity is used to assess the functional significance of renal arterial abnormalities. We now use the radioimmunoassay technique to measure PRA. Blood samples are collected in ethylenediaminetetraacetic acid, which inhibits plasma peptidase activity and also serves as an anticoagulant. The sample must be immersed immediately in an ice bath at 0° centigrade and centrifuged within 10 minutes in a refrigerated centrifuge. Once centrifuged, it can be frozen and kept for months until the radioimmunoassay is performed. Essentially, the technique consists of incubating the plasma at pH 5.5 for three hours and then performing a radioimmunoassay of the angiotensin I generated.

There are several critical conditions (posture, sodium intake, medications) for collection of blood specimens that must be controlled for accurate assay of PRC or PRA. We are still unclear about the action of various antihypertensive agents on both the plasma renin level and the release of renin substrate. This may cause problems because many of the patients taking these agents are severely hypertensive, and discontinuance of medications is not advisable and may be hazardous.

The value of measuring peripheral PRA or PRC has been discussed extensively. Measurement of peripheral PRA or PRC is useful if blood is collected after the patient has been supine for eight hours and again after he has stood or sat for four hours. These values will screen out patients with elevated or subnormal levels. PRA or PRC can then be measured in the screened patient after salt restriction and the additional stimulus of diuretic therapy. There is no question that the finding of a low plasma renin after salt depletion, and possibly after the stimulus of a diuretic agent, strongly suggests that some primary adrenal disease may be present with excessive mineralocorticoid activity. A very high renin level, conversely, suggests a renal etiological background of concurrent hypertension. The PRA or PRC level is not always diagnostic for renovascular hypertension or primary aldosteronism since patients and normal subjects can have an exaggerated response to posture. Approximately 20 percent of the patients with essential hypertension can also have subnormal levels of renin even after salt restriction and diuretic therapy.

The reason for the frequency of low PRA in patients with essential hypertension is not clear. We have studied deoxycorticosterone secretion in many patients with essential hypertension, low PRA or PRC levels, and normal levels of urinary aldosterone and, as yet, have found no abnormality. Woods²¹ administered an adrenal blocking agent, aminoglutethimide, to such patients and observed mild improvement of hypertension in some, suggesting that there may possibly be some other adrenal factor. Of great interest is the recently discovered steroid 18-hydroxydeoxycorticosterone. It was first identified in rats and mice, was subsequently measured in camels and now finally has been measured in man. It is secreted in amounts very much like those of al-

TABLE 2.—Plasma Renin Activity Measurements in Peripheral and Renal Veins*

Patient No.	Control Periph- eral PRA† (ng/ml/3 hr)	PRA* Levels (ng**/ml/3 hr)			Lesion‡
		Inferior Vena Cava	Left Renal Vein	Right Renal Vein	
1	0.4	0.5	0.7	0.8	Aldosterone-producing adenoma
2	7.1	5.3	7.7	5.7	Small kidney—right
3	13.4	15.5	45.4	13.0	Fibromuscular dysplasia on left
4	76.0	49.2	88.4	94.6	Juxtaglomerular hyperplasia
5	13.5	12.4	15.8	12.2	Severe arterial stenosis on right
6		25.5	190	370	Severe bilateral arterial stenosis, greater on the right side
7		24.4	20.9	85.5	Renal artery stenosis on right side
8	20.9	30.8	28.6	24.2	Bilateral fibromuscular dysplasia
9			2.6	1.4	Bilateral fibromuscular dysplasia
10		1.2	1.4	1.2	Bilateral fibromuscular dysplasia
11		9.6	12.2	13.6	Bilateral fibromuscular dysplasia
12	2.5	3.4	3.3	3.6	Unilateral pyelonephritis of right kidney
13	30.6		26.5	25.7	Bilateral pyelonephritis, small right kidney
14		24.9	29.0	81.0	Pyelonephritis, hypoplastic right kidney

*PRA=plasma renin activity

**nanograms

†Measured in the inferior vena cava on the day before renal vein studies.

‡These cases were chosen at random to illustrate the variety of lesions in which measurements of renal venous renin activity have been undertaken in our laboratory. Operation was performed only in Cases 1,3,5,6 and 7 and improvement in the hypertension was observed postoperatively in all five cases. Operation was not performed in the remainder of the cases because of inoperability (bilateral fibromuscular dysplasia) or because the hypertension was well controlled with antihypertensive medications and nephrectomy would have further diminished the already impaired renal function (Cases 2,12,13,14). Patient No. 4 was obviously not a candidate for operation.

dosterone, but its biological activity in man is not clear.

Plasma renin activity is of great importance when measured in a peripheral vein and both (bilateral) renal veins of patients with renovascular hypertension. Of the many techniques available, this is the best method for determining which side the lesion is on.²⁵⁻²⁸ A high peripheral PRA level and a bilateral discrepancy in the PRA levels in the renal veins have successfully located the lesion preoperatively (Table 2) and resulted in cure or improvement (more than 80 percent of cases) after arterial repair or unilateral nephrectomy. Catheterization of the renal veins is a relatively simple procedure. With unilateral renovascular disease, the ratio of the difference between an abnormal and a normal side is usually 1.5 to 2.0 or greater. No such difference is observed in patients with bilateral renovascular disease. One should be aware, however, that the PRA level can vary with stress and discomfort. On several occasions we observed quite different and much higher peripheral vena cava levels of PRA when blood was collected during renal vein renography than when specimens were obtained after fasting and overnight recumbency.

Some investigators attempt to bring out differences in the two sides by tilting the body and administering hypotensive agents, such as diazoxide or hydralazine. At times this can prove very helpful.

Our measurements of bilateral renal vein PRA in patients with a variety of clinical conditions are shown in Table 2 and range from the very low levels in primary aldosteronism (Patient No. 1) to the high levels in juxtaglomerular cell hyperplasia (Patient No. 4). The classic elevation of peripheral PRA with differential elevation of renal vein PRA in Patients 3, 6, and 7 with renovascular hypertension indicates that benefit from surgical repair can be anticipated. Whereas in Patient No. 5, who also had renovascular hypertension and elevated PRA levels, the renal vein PRA levels were similar, suggesting a questionable response to operation. In the patients with diffuse or inoperable bilateral fibromuscular dysplasia (Patients 8 to 11), PRA levels varied from normal to elevated and were similar bilaterally, suggesting that renin may not be the sole determinant of hypertension in this disorder. We are especially interested in employing this comparative PRA approach to gain more information

about other renal diseases accompanied by hypertension without renovascular abnormalities. Patients 2 and 12 had a small kidney and unilateral pyelonephritis, respectively, and normal but bilaterally similar renal vein PRA levels. Patients 13 and 14, who had bilateral pyelonephritis associated with a small kidney, pose particular problems. In these patients assessment of renal blood flow and total functional renal mass is critical before making the decision of surgical intervention.

One cannot help being impressed by the fact that bilateral measurement of renin in the renal veins can, and frequently does, identify small segmental lesions and often intrarenal lesions that may escape even the scrutiny of an expert radiologist and the split-function study. These studies may direct more intensive radiological investigation of the abnormal kidney detected by increased plasma renin levels.

One must be cautious not to over-interpret renin measurements. Although they can identify the abnormal kidney, renin may not be the specific cause of the hypertension. Despite this limitation, it is entirely possible that bilateral measurement of renin in the renal veins may in time be the more logical next step after an abnormal intravenous pyelogram than the critical arteriogram in the evaluation of renovascular hypertension.

Summary

To summarize, the two most common causes of correctable hypertension are an aldosterone-producing adenoma and renovascular hypertension. The diagnosis of primary aldosteronism is established by the demonstration of elevated aldosterone production that is not suppressible by deoxycorticosterone acetate. A low peripheral level of plasma renin activity (PRA) is corroborative but not diagnostic, but an elevated level of PRA rules out primary aldosteronism.

The diagnosis of renovascular hypertension is only suggested by an elevated peripheral level of PRA. An abnormal intravenous pyelogram and differential elevation of renal vein PRA are diagnostic, they identify the abnormal kidney, and they may indicate preoperatively the results of corrective operation.

The use of bilateral measurements of renal vein PRA in evaluating other types of renal dis-

ease associated with hypertension may prove most helpful in assessing the role of renin and in further identifying the abnormal kidney.

TRADE AND GENERIC NAMES OF DRUGS

Florinef® fluorohydrocortisone

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Important Advances in Clinical Medicine

Epitomes of Progress -- General and Family Practice

The Scientific Board of the California Medical Association presents the following inventory of items of progress in General and Family Practice. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in General and Family Practice which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General and Family Practice of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

Drug Exposure in the Hospital

If you wish to start a lively and interesting conversation among physicians, ask the question: "If you were limited to only three medications that are available today, which ones would you use?"

The answers are sure to differ, depending on the area of practice and the personal philosophy of the individuals concerned. The psychiatrist may include various psychotropic drugs that would be completely ignored by the surgeon. The dermatologist may not choose any of the

analgesics that would be the surgeon's first choice, etc.

In these circumstances, the list of medications to which the average hospitalized patient is exposed would be almost humorously shortened. As a matter of personal interest, check the number of medications ordered on your own hospital patients' charts and notice that they will vary from three to twenty.

When you consider the various effects of these medications on the body, coupled with their effects on each other, and the secondary and tertiary effects of *that* reaction, the mind is staggered at the possibilities. (As the number of drugs increases, the chance of a drug reaction increases in a geometric progression).

Of more practical importance is that approximately 5 percent of hospital admissions are for

drug reactions and approximately 15 percent of hospital patients have a drug reaction while in the hospital. Since the trend seems to be to use more and more different medications, I suggest that each one of us order medications as if we were to be confronted by a colleague and asked to justify its presence on the order sheet.

A. J. WYATT, M.D.

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Skillful Neglect

One of the most difficult decisions in medicine today is when the life of the patient should be maintained artificially.

Today's physician is faced with more and more methods of maintaining "life" and preventing "death." These terms are under constant re-defining as we now find that the old criteria of life and death no longer are sufficient.

The determination of life support becomes a social, family, moral and economic issue. When has useful life ceased and mere existence begun? How often have you had a patient ask, "Please, why don't I die?" Naturally this can occur in a mentally ill patient who can be helped; but what of the elderly, senile or physically incapacitated patient who you know cannot be restored to a useful or satisfying life?

The moral decision of euthanasia cannot be made ethically today, but are "heroic measures" indicated in these cases? I feel a very beneficial attitude is one that was presented to me when I was in medical school by one of my senior professors who said that at some time in life the best therapy is "skillful neglect."

SIMON C. BRUMBAUGH, JR., M.D.

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Coronary Risk in Post-Menopausal Women

The presence of thyroid antibodies in post-menopausal women is a predisposing factor to coronary artery disease. The presence of thyroid antibodies in asymptomatic thyroiditis is correlated with a 2.4 times increased frequency of coronary artery disease in women of comparable age. The reversal of the usual sex ratio, which normally shows males having coronary artery disease at twice the rate for females, is reduced to a one-to-one ratio if the female shows antibodies for thyroiditis.

The mechanism for the increased risk to females with asymptomatic thyroiditis may partially be explained by the elevated serum cholesterol in this group. For some unknown reason, males with this condition did not have a raised serum cholesterol value nor an increased incidence of coronary artery disease. Further evaluation of this risk factor seems worth while.

JOHN F. BRIDGEMAN, M.D.

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Triiodothyronine

The ability to easily assay triiodothyronine (T_3) may explain the present problems in correlating clinical symptoms with the various thyroid function tests.

A new clinical entity has been described, consisting of thyrotoxicosis with raised serum concentrations of T_3 but normal total thyroxine concentration. In addition, these patients may have normal radio-iodine uptake. This has been seen even in patients with a normal level of thyroxine-binding globulin (TBG) and thus a normal free-thyroxine concentration.

An adequate assay of T_3 would explain the

euthyroid patient who has a low serum thyroxine concentration, and conversely the panhypopituitarism patient with a normal standard thyroid-function test. It may well be that a simple T₃ assay will be the Rosetta Stone which correlates the often contradictory laboratory tests and clinical finding in thyroid malfunction.

JOHN F. BRIDGEMAN, M.D.

REFERENCE

Triiodothyronine (Editorial): *Lancet* 1:898-899, May 1, 1971

Some Implications of Zero Population Growth

The widespread advocacy of zero population growth as a means of alleviating the effects of rampant pollution of our environment and destruction of our natural resources has profound implications for society and for the medical profession in particular. Already much of the medical profession has joined the crusade by prescribing the pill, by inserting the intra-uterine device, and by carrying out abortion.

The economic implications of zero population growth, when accomplished only by limiting births, were brought home strongly to me on a recent visit to Denmark. Informed citizens of Denmark point out that they have achieved zero population growth in that country since World War II. In a country which offers cradle-to-grave security, free medical care, and old age retirement benefits they are beginning to foresee the day when there will be an insufficient number of young productive citizens to support the economy. People in their twenties and thirties are asking who will support them in thirty years when they are eligible for retirement benefits.

It may not be feasible to obtain zero population growth by limiting infant input alone. The immediate implication for medicine is a reassessment of our traditional ethics and our accepted purpose of sustaining and prolonging life. The primary objective for medicine must perhaps be changed to the improvement of the quality of life rather than the prolonging of life.

Are we in medicine beginning to mature enough to discuss objectively methods of limiting

the duration of life for the totally demented or totally disabled? Perhaps physicians must accept and respect the wishes of many patients that they be permitted to live to the fullest while in possession of all their faculties and then be permitted to die with dignity without heroic measures used to prolong their mere existence.

Are we in medicine ready for the implications of zero population growth?

J. BLAIR PACE, M.D.

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Use and Abuse of Sedatives

The sleeping pill or sedative is part of our medical tradition. If we admit a patient to the hospital and do not order sleeping medication, the nurse is certain to call us and point out the oversight. Patients expect or demand that they be given something for sleep.

Aside from the potentials for overdose and suicide, the widespread use of hypnotics and sedatives is far from being an unmixed blessing. Disturbance of the sleep pattern is now widely recognized as a hallmark of depression. Hypnotics and sedatives of the traditional kind are also depressants in terms of our modern psychopharmacology. It is doubtful that the depressed patient given a barbiturate each night for sleep will actually improve and quite probable that he will become increasingly more depressed. The potential for abuse, overdose, and habituation is greatly increased in the depressive.

A surprising number of people who have had a recognized depression treated with tricyclic anti-depressants have commented on the marvelous improvement in their sleep pattern. After the spell of depression is over many of them keep a few tablets and use one now and then as a sedative. This opens the exciting possibility that one could treat the disturbed sleep pattern with a medication which would improve the mood of the patient as well as the sleep pattern. This might obviate overdose problems, suicidal attempts, and habituation effects.

A very stubborn type of insomnia occurs in the acutely anxious patient. Traditional hypnotics have done little for anxiety. Modern psychotropic drugs that are more specific for anxiety have tended to let the patient sleep quite naturally and normally without significant depression or hangover.

It is time for a whole new look at the sedative/hypnotic prescribing habits of physicians.

J. BLAIR PACE, M.D.

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The Pill and the Teenage Girl

Today the busy family practitioner is repeatedly facing the problem of when to prescribe the pill. The problem is increased in teenage patients because the medical decision must also be weighed with the social factors—that is, promiscuity, venereal disease, pregnancy and, last but not least, parental consent.

I won't discuss the medical concerns of giving the pill to immature females, for this is a problem regardless of marital state. The more difficult ethical or legal decision relating to unmarried teenagers is a concern of all family physicians.

The law in California now permits married minors or emancipated minors—that is, anyone over 15 years of age living separate and apart from his parents or guardian and who is managing his own personal affairs (regardless of source of income)—to give consent to furnishing hospital, medical and surgical care to himself.

The physician may with or without the minor's consent notify the parent or guardian of the treatment prescribed.

The law, therefore, places all the responsibility of the decision on the family doctor. The physician, therefore, must decide the moral questions as well as the medical problems. I wonder if society is once again avoiding a difficult decision

and shifting responsibility from the parent to the doctor as many parents are doing with drugs and the juvenile authorities.

SIMON C. BRUMBAUGH, JR., M.D.

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- Teenage Patients—Their legal rights and yours. *Medical World News*, pg 49, May 14, 1971

Risk of Breast Cancer

The risk of breast cancer in women seems to be most significantly related to parity. Single women have a higher incidence than married women. Non-parous married women have a higher incidence of breast cancer than parous women. There is a tendency for risk of breast cancer to generally decrease with increased parity.

Further examination of the data shows that a significant factor is the age of the woman when she has her first baby. The younger the mother is when she has her first child, the less the chance of breast cancer. The proposition that lactation itself protects from breast cancer is not borne out. This data still does not explain the even more dramatic geographic disparity in breast cancer rates.

JOHN F. BRIDGEMAN, M.D.

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Hippie Hepatitis

The diagnosis of subclinical or anicteric hepatitis is often suggested on the basis of symptoms and laboratory findings present on routine psychiatric hospital admissions of teenagers from hippie cultures who have a strong history of drug abuse, both oral and parenteral, and it is thought that this condition is much more prevalent than previously suspected in this cultural setting. In the absence of jaundice, the symptoms of fatigue,

flu-like symptoms and anorexia are often difficult to distinguish from mild depression—ubiquitous among such cultures—and/or undernutrition or malnutrition. Low grade fevers are not uncommon in hospital admissions, particularly when there is associated subacute bronchitis or pelvic inflammatory disease—again, often the case with this group. It is thought that many commune cultures are fairly comfortable with diagnosing and managing infectious hepatitis among their members, since most are cognizant of its usually non-fatal, limited and relatively benign course. This, coupled with the realization that medical science has little in the way of real relief or cure to offer, means that most cases of “the hep” are not seen by doctors except by chance as in the situation where hospital admission for other reasons becomes mandatory. Routine chemical panel screening tests become mandatory at that point.

NORMAN C. HEADLEY, M.D.

REFERENCE

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Epidemic Gonorrhea

Today in California the problems of venereal disease are becoming the major public health problem in young people (under 25 years). Half a million cases of gonorrhea in California are predicted by the State Department of Public Health this year.

Venereal disease is the Number One reportable communicable disease nationally and is primarily (80 percent) treated by the private physician. We must suspect it, recognize it, diagnose it, and treat it.

In addition to this, we must attempt to prevent it. The International Venereal Disease Symposium in St. Louis stated that “the lag between public concern and organized action must be shortened.” We cannot afford to be Victorian in our attitude toward VD when sexual permissiveness continues to increase.

The primary factors are awareness of the problem, education of the public, detection of cases, adequate treatment and contact follow-up. The

family physician can be instrumental in controlling this epidemic.

SIMON C. BRUMBAUGH, JR., M.D.

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San Diego's Health. San Diego County Department of Public Health Bulletin, 19: April 1971

International Venereal Disease Symposium, St. Louis, 1971—Co-sponsored by the American Social Health Association and Pfizer Laboratories

Incidental Hypokalemia in Ambulatory Patients

The increasing use of automated laboratory screening panels are identifying more patients with incidental hypokalemia. Physicians are alert to the possibility of hypokalemia in digitalis intoxication, in gastrointestinal fluid loss and in the potential hypokalemia resulting from diuretic administration.

But hypokalemia may occur as a result of adrenal steroid therapy and in the intrinsic adrenal diseases Cushing's syndrome and primary or secondary aldosteronism. Other causes are primary renal disease and ingestion of outdated tetracycline (although the mode of action in this latter cause is not known).

The gravity of unrecognized hypokalemia is highlighted by reports from coronary care units of patients admitted with repetitive cardiac arrhythmia who do not respond to any therapy, including countershock, until the electrolyte deficiency is recognized and treated.

Physicians should be alert to other hidden causes of hypokalemia—that is, laxative-induced diarrheas, self-induced vomiting, and persistent rectal discharge from colon disease.

In non-emergency cases, hypokalemia can be treated orally by the administration of 40 mEq of elemental potassium per day. Further adjustment of dosage should be determined by electrolyte monitoring. Caution must be used in potassium supplementation, as the amount of deficiency or daily dosage is not accurately known.

WILFRED SNODGRASS, M.D.

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Daniell HW: Arrhythmia in hypokalemia. *N Engl J Med* 284: 1385, June 17, 1971

Learning and Behavior Disorders In Children

Skilled kindergarten teachers, psychologists, and informed parents have begun to recognize the potential "problem child" early in his school career. Advice and counseling by the physician and the administration of medications can be of inestimable benefit to such children.

From the educational point of view, distractibility and short span of attention are the most significant characteristics of these children who have been given a wide variety of labels including hyperkinesia, dyslexia, hypokinesia, minimal brain damage, minimal brain dysfunction and others.

A detailed developmental history, filled out by the parents at home, can save the physician time and will suggest areas of investigation. The physical examination will usually present only the so-called "soft signs," such as poor coordination, poor balance, poor performance of finger-to-nose or heel-to-shin. Some physicians and psychologists place great emphasis on the finding of awkward dyskinetic creeping.

The hyperkinetic child is benefited by the administration of sympathomimetic drugs. Amphetamines have the advantage of being available in long-acting dosage form. Ritalin® (methylphenidate) has the advantage of a better quality of control and a higher percentage of success. Stimulant drugs do not produce euphoria in hyperkinetic children and are, therefore, non-habituating.

Responsible administration of helpful medications to children with learning and behavior disorders is not scandalous but rather highly desirable and commendable. There is a need for more widespread and more specific application of medical and pharmacological assistance in the problem of learning and behavior disorders.

J. BLAIR PACE, M.D.

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Increasing Problem of Malaria

Malaria is the most prevalent disease in the world today — 200,000,000 cases annually. The disease is seen throughout the world, especially in Asia. When one considers how many servicemen are rotated from this area each year, the number of cases in the United States is remarkably small, considering that the *Anopheles* mosquito is present in many areas of the United States.

The ideal method of protection of both the returning soldiers and the population in this country requires the continuation of preventive medication for a period of two months after return from an endemic area. This is rarely done, and perhaps of more significance is the fact that for the two million civilian tourists, malaria protection is rarely, if ever, practiced.

As several recent articles have indicated, the number of domestic cases is increasing. There were 54 reported cases of malaria in the United States in 1959, and slightly more than 3,000 cases in 1970. Although most of these cases were associated with returning servicemen, an interesting sidelight of the disease is the transmission to civilians by the use of needles for heroin injection. This method of infection has been implicated in one recent episode in Central California.

In our search for disease and in its treatment one should keep in mind that malaria is far from uncommon in the jet age; and in cases involving periodic spikes of fever, especially if associated with anemia, this ancient disease should be considered in the differential diagnosis, especially since the falciparum variety may be fatal and require somewhat specific therapy.

A. J. WYATT, M.D.

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Barrett-Connor E: Malaria—An "imported" disease to be reckoned with in the U.S. *Calif Med* 115:19-24, Aug 1971

The Use of Packed Red Cells In Transfusions

Heretofore whole blood has been considered the primary agent for the treatment of a variety of anemias. With the increasing successful fractionation of whole blood, physicians are obligated to choose blood components with more specificity.

When a blood transfusion is contemplated, packed red blood cells rather than whole blood should be given primary consideration. The transfusion of whole blood should require evidence of its need—that is, hypovolemic shock.

The pathophysiology of impending cardiac decompensation, hepatic cirrhosis, uremia, acute burns, anemia associated with bone marrow fail-

ure, debilitated, aged or patients of small size may be complicated by whole blood transfusions. In most cases, preoperative anemia and surgical blood loss can best be treated with packed red blood cells or balanced salt solution or both.

Red blood cells are the only blood component that can increase the oxygen-carrying capacity of the patient's circulation. Plasma proteins, platelets, electrolytes, leukocytes, coagulation factors and metabolic wastes are inescapable by-products given when *whole* blood transfusions are used to increase the oxygen-carrying capacity of blood.

Probably 75 to 80 percent of patients who require transfusions should receive packed red blood cells.

WILFRED SNODGRASS, M.D.

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National Health Insurance

Caveat Emptor

A DECISION TO ENACT SOME kind of health insurance fairly soon has apparently been made. The proposals before the Congress and the presentations at the hearings being held at the time of this writing offer a wide spectrum of different and largely incompatible attitudes and approaches. The rather sudden decision to proceed at this time suggests that what will be enacted has now been more or less decided, although what this is has yet to be revealed. Assuming this is the case, we say *caveat emptor*, let the buyer beware, for there is a great deal not yet known either about what should be purchased or what it should be worth and to whom.

National health insurance will be buying something for which there is as yet no clear description or specification. Is it health, as the term itself would imply, and if so what is the definition of health to be used? Or is it health care, and if so precisely what is involved in this, or is it medical care, and if so how much of what for whom? Much of what is to be purchased, including physician-patient relationships, has yet to be defined, and its value has yet to be determined in ways which will be acceptable and standard across the nation. Until questions such as these can be answered, confusion, dissatisfaction and waste of dollars are inevitable.

The decision to proceed with national health insurance is considerably the result of rhetoric which has unfortunately been based largely upon myths and slogans which have been repeated so often that they have now become accepted as truisms. The untruth of many of these statements and assumptions which seem to underlie so many

of the proposals now under consideration, will sooner or later, and after millions or billions of dollars, become evident. The sad reality will be that dollars and scarce resources which could have been more wisely used will have been wasted in obedience to myths which have been accepted as truths.

So far no realistic thinking is apparently being given to what the relationship can be between scientific and technical progress and the numbers and kinds of services which will have to be paid for by national health insurance. As science and technology progress, services will become more numerous and more frequently rendered, and they will cost more. This can only be curtailed by reducing support for medical research as a kind of preventive measure, or by restricting the kinds, frequency or expense of the services to be rendered. Actually both have already begun. The federal government has substantially reduced its support of medical research and the state restricts the services available to patients under its Medi-Cal program for the care of indigents. Yet if national health insurance is to be in the long run good for the nation, it seems that it should somehow encourage more research rather than less, and more and better patient care services rather than less.

There are many indications that national health insurance will propose more organization and system in the delivery of medical and health care services with the intent of producing more services at less cost. Experience would suggest that this is likely to prove a contradiction in terms, since more organization and more delegation and distribution of tasks tends to increase costs although it may also increase the number of services rendered. However, the opinion that costs can be reduced by more system is so widely held that national health insurance may squander considerable money and other resources in pursuit of this mirage.

Finally, one wonders how much national health insurance will be concerned with either

consumer or provider satisfaction with the plan or its services. There is little evidence so far that either the consumer or the provider has been consulted to any extent in the preparation of proposals, yet it stands to reason that the one must receive its benefits and the other deliver them, and that both must be satisfied if things are to go smoothly and well.

The writer of this editorial is fully aware that what is said here or anywhere else is not likely to have much influence at this late date. But it is to be hoped that those who have the power and determination to enact national health insurance, whether it be this year or next year or sometime thereafter, will give some thought to the enormous impact of what they are doing, to the relative absence of firm data upon which to base this action, and to the real possibility that whatever controls and restraints they impose may have the effect of reducing rather than increasing the amount of health care which would otherwise have been rendered to the people of this nation.

The California Medical Association along with many others believes that some form of national health insurance is now needed, and along with many others CMA has submitted its own proposal to the Congress. It is quite obvious that none of these proposals will be accepted as they stand. We now await with interest and no little apprehension the apparently imminent revelation of the plan for national health insurance which will be debated and probably eventually enacted in some form by the Congress. We know that it can only be based on insufficient and often inaccurate information and on inadequate data since the necessary information and data simply do not exist. So again we say *caveat emptor*.

—MSMW

Renal Allograft Rejection

THE DIAGNOSIS OF THE REJECTION process in a human renal allograft remains a baffling and frustrating problem. To date, there exists no satisfactory method of diagnosing the rejection process itself, and, therefore, we must fall back

upon functional changes in the transplanted kidney itself. Because such changes may be mimicked by a number of processes other than rejection or the kidney affected by other insults in addition to rejection, the problem of when to treat the allograft rejection, and how vigorously, is constantly with the clinician who cares for such patients. The tools available for suppressing or reversing rejection process are much too dull and nonspecific. In addition to affecting the rejection process itself, they impair a good many functions which protect the integrity of other organs. Thus, azathiaprine, the basis of present immunosuppressive therapy, impairs protection against bacteria, yeasts, and probably even the spontaneous development of lymphoid tumors. Massive doses of corticosteroids, which are the only truly effective method of reversing rejection, obviously impair wound healing, the localization of infection, and cause gastrointestinal bleeding. Were one to develop an effective, simple, and infallible test for the rejection of a kidney transplant, one might treat the process earlier and with smaller amounts of immunosuppressive agents, thus preventing damage to the allograft and to the host as well. Unfortunately, morphologic and functional changes which may be confused with changes not related to the rejection process, are the best, but still unsatisfactory, indices of kidney rejection.

This is the issue to which Mr. W. J. Dempster of the Royal Post Graduate Medical School of London addresses himself in an article elsewhere in this issue of CALIFORNIA MEDICINE.

However, his discussion includes considerably more than is indicated by the title of his article. Many of his opinions will not be shared by other workers in the transplantation field—but this has never deterred Dempster from expressing them. He has been in the business of transplanting kidneys for a long while, certainly from the beginning of the modern era, and he writes with the assurance which springs from long familiarity with the problem. His were some of the earliest and most fundamental observations on the functional and pathologic characteristics of the transplanted dog kidney. I was fortunate in being able to visit him in 1953 and observe his work at first hand. At that time, his laboratories were situated in the magnificent Buxton Browne Research Farm, the site of Charles Darwin's former home. His animal experiments were carried out

largely with greyhounds, since he felt that the inbreeding and care taken of these animals might minimize random differences in antigenicity and decrease the risk of parasitic infestation. It was a privileged and productive visit for me who found the quality of Dempster's wine cellar almost equal to the excellence of his surgical experiments.

The major thrust of Dempster's essay is that "rejection, acute or chronic, is the onset of renal failure due to a series of changes in the vasculature of the allotransplanted kidney leading to inadequate perfusion." This, I believe, is critically important and explains the majority of most of the functional and pathologic changes which are seen in rejecting kidneys. Vessels of all calibers are involved, including the glomerular capillaries. The violence and the extent of the reaction will, of course, vary between different donor and recipient pairs. In related individuals, this appears to be in large part a function of the histocompatibility differences between the donor and recipient, a point with which Dempster takes issue. Acute involvement of the vasculature with aggregation of platelets upon denuded basement membranes, the release of vasopressor substances, the production of fibrinogen and fibrin, and ultimately either thrombosis of the vessel or healing of fibroblastic invasion and fibrosis are general characteristics of the process. Obviously, such effects must be reflected in changes in renal function. These are discussed in some detail by Mr. Dempster. Quite correctly he stresses our inability to correlate morphologic change and functional change. He points out that common concomitants of rejection are hypertension as well as fever, anorexia, and malaise of unknown etiology which are the more important because they may simulate an infectious process to which such patients are so sensitive. It is worth noting that the hypertension occurring during the course of rejection is one of the few hypertensive states which improves dramatically with massive doses of corticosteroids.

Decreases in perfusion of the kidney are, of course, the hallmark of rejection. Changes in the distribution of blood flow may occur before decrease in total blood flow, and this can be measured by the washout of radioactive xenon and by the renal arteriogram.¹ If such procedures could be done at frequent intervals without harm to the patient, they might well give us the earli-

est indication of the rejection process. The radiohippuran renogram gives an index of changes in renal perfusion and urine formation, but unfortunately these are relatively nonspecific. However, they do show improvement or deterioration of renal function and, as such, may be valuable in following a patient being treated for presumed rejection. The arteriogram nicely delineates the changes both in acute and chronic situations.

A major problem is a period of anuria which may ensue following transplantation, particularly of a cadaver kidney. This oliguria or anuria may reflect only ischemic damage, but the threat of rejection is ever present. Here the radiohippuran renogram may be helpful but not definitive since it is known that in kidneys anuric as a result of acute ischemic damage, total renal blood flow may be maintained to the extent of 50 to 60 percent of normal. Oliguria may be due to rejection, or thrombosis of the major vessels, or obstruction or a ureteral leak. The renogram and the arteriogram are particularly helpful in differentiating rejection from thrombosis of the renal artery or from obstruction. These problems are discussed in some detail by Dempster.

There is much in his discussion of mechanisms to titillate the renal physiologist. For example, mild hydroureter and hydronephrosis due to denervation of the ureter are suggested as a cause for decreased sodium absorption in the proximal tubule and the post-transplant diuresis which is so frequently seen. Dempster believes that, "an expanded extracellular fluid volume is not a major factor [in the diuresis] as the GFR is frequently grossly subnormal for some weeks." However, there is much evidence that expansion of the extracellular fluid volume may be associated with a natriuresis which is independent of the glomerular filtration rate. The proteinuria is described as tubular in origin, and it is suggested that edema of the hilar fat with pressure on the renal vein may be the cause of the first drop in solute excretion seen. The clinician will be disturbed to learn that Dempster believes that "whether kidney transplant recipients are positive or negative for HLA antibodies is irrelevant clinically." It is disappointing to learn that Dempster has not "been able to confirm" the "correlation between antigens of leukocytes and skin" as reported by Medawar and others.²

Later functional abnormalities of renal allografts which deserve mention are the prolonged

salt-wasting syndrome and characteristic renal tubular acidosis. All of considerable interest and almost certainly resulting from rejection process, these entities do not appear to be associated with a bad prognosis.

The problem of hyperacute rejection of the kidney receives and deserves extended treatment. Most workers will agree that clearly demonstrable lymphocytotoxic antibodies against the lymphocytes of the donor, which can be demonstrated in high titer in the serum of the recipient, will result in a rapid destruction of the transplanted allograft characterized by small vessel thrombosis and necrosis and interstitial hemorrhage. Dempster's scepticism of the role of these anti-human antigen antibodies is in part justified by the fact that not all such "sensitized" patients do this. Furthermore, we are seeing with increasing frequency post-transplant anurias presumably on the basis of rejection which occur within three or four days of transplantation in patients in whom no preformed antibodies could be demonstrated by any of the currently available tests before transplantation. One cannot be sure whether we are dealing with technical problems or with an inability to characterize and detect previous sensitization to donor tissue.

Quite correctly Dempster emphasizes the necessity for adequate hydration of the donor before transplantation. Restriction of salt and fluid in the surgical patient is a time-honored procedure. However, it is clear from both clinical and experimental evidence that the production of adequate hydration and adequate urine flow before induction of anesthesia is important in preventing ischemic damage to the kidney. It is the custom in many transplant groups to hydrate the prospective donor by vein and to maintain him on a high salt diet before operation. That these maneuvers take part in suppressing renin formation which might play a role in acute vascular spasm has been suggested.

Techniques are badly needed for detecting smoldering subclinical rejection which may result in pronounced vascular change, nephrosclerosis and renal failure two to three years post-transplant without evidence of acute rejection at any time. Similarly, although this is questioned by Dempster, there are well authenticated cases of primary glomerular involvement which may present as a full-blown classical nephrotic syn-

drome—the result of immunologic attack upon the glomerular capillaries.³

The renal functional changes then, with the possible exception of those changes in the renal arteriogram and distribution to blood flow, remain relatively nonspecific. Were it possible to correlate changes in renal function with some single indicator of the rejection process *per se*, our problem would be simplified. To date, no such test exists but approaches such as spontaneous transformation of peripheral lymphocytes hold promise for the future.

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The Nephrotic Syndrome

IN THE NOVEMBER issue of this journal,¹ a splendid staff conference from the University of California Medical Center in San Francisco summarized just about everything currently known about that most intriguing of renal disorders, the nephrotic syndrome. As Dr. Earley and his colleagues point out, this term refers not to any particular disease or histological entity, but rather to a functional disturbance, the essence of which is an excessive loss of plasma proteins through a leaky glomerular filter.

Present nosological concepts of this condition have been shaped largely by the numerous clinicopathological studies that began about twenty years ago following the introduction of percutaneous needle biopsy of the kidney. More recently, the application of electron microscopy and immunofluorescent staining techniques has made possible a more sophisticated exploration of the histopathological basis of the nephrotic

syndrome, and this work has been supplemented by elegant studies of the biochemical and physiological disturbances associated with the nephrotic disorder.

It is now apparent that the glomeruli can become leaky as the result of a wide variety of pathological processes, some of which are part of extrarenal or more generalized disorders and others of which are primary diseases of the kidney. The relative incidence of these various etiologic backgrounds is influenced by geographic factors. Thus, the most common cause of the nephrotic syndrome in parts of Africa probably is the nephritis associated with quartan malaria,² but in the United States and in Western Europe the majority of cases are caused by a group of primary glomerular diseases often referred to collectively as the "idiopathic nephrotic syndrome" (INS). As the term implies, little is known about the cause of INS, but this group of glomerular diseases seems to be distinct from that form of chronic glomerulonephritis which follows an attack of acute poststreptococcal glomerulonephritis. Poststreptococcal chronic nephritis is, in fact, a far less common cause of the nephrotic syndrome than is INS.

About one-third of adults with INS reveal little or no change in the glomeruli on examination by conventional light microscopy, and they show only slight fusion of the foot processes of the glomerular epithelial cells on electron microscopy. To this type of case, more common in children than in adults, the term *lipoid nephrosis* is usually applied. The remaining patients with INS are said to have *membranous* or *proliferative* glomerulonephritis because they show varying degrees of thickening of the glomerular capillary wall, or proliferation of endothelial or epithelial cells, or both.

Although it is not yet clear whether the different histological types of INS represent separate pathological entities, much recent evidence suggests that lipoid nephrosis may be an entity quite distinct from idiopathic membranous or proliferative glomerulonephritis. Both of the latter two forms of INS are characterized by electron-dense deposits along the basement membrane, which contain complement and 1gG, 1gM or 1gA. These deposits are said to represent antigen-antibody complexes, which are thought to play a key role in the pathogenesis of the pro-

gressive glomerular disease. On the other hand, no such deposits have been found in most instances of lipoid nephrosis, and that may be the reason this form of INS has a much better prognosis than the others. Recently, it has been reported that 1gE is deposited along the basement membranes in lipoid nephrosis,³ thus raising the possibility that some special type of allergic mechanism may be involved.

The mere presence of immunoglobulins in the glomeruli of patients with INS does not, of course, prove that immunological phenomena play a primary role. It is instructive to remember that acute thrombosis of the renal vein may be associated with deposition of immunoglobulins in the glomeruli⁴ although there is reason to believe that it is usually the thrombosis rather than an immunological disturbance that initiates the renal damage. A similar comment can be made about the presence of immunoglobulins in the damaged renal arterioles of some patients with severe arteriolar nephrosclerosis.⁵ Thus, before the full significance of immune complexes in INS can be assessed, it will be necessary to learn much more about the antigens and antibodies that may be involved and the nature of the events that trigger the whole pathological sequence.

Most, if not all, of the functional disturbances characteristic of the nephrotic syndrome apparently follow from the primary glomerular defect in protein filtration, but many important questions remain to be answered about the mechanisms involved. One of the most puzzling of these concerns the factors determining the level of serum albumin. If urinary loss of protein were the only reason for hypoalbuminemia, why is there so little correlation between the serum level and the rate of excretion of albumin in the urine?

Looking for other causes of the serum protein deficit, several investigators have studied the various aspects of albumin turnover in nephrotic patients. The results to date do not justify firm conclusions, but some tentative answers are suggested by a notable study from Copenhagen.⁶ Nineteen of 30 patients with various types of adult nephrotic syndrome were found to catabolize an increased fraction of their total intravascular albumin pool each day. In the remaining 11, this fractional catabolic rate was normal. Only in this latter group, therefore, was the total

degradation of albumin reduced, as would be expected with a contracted pool and reduced serum concentration. These observations were interpreted to imply that albumin degradation in the kidney is relatively increased in some nephrotics, perhaps due to increased tubular absorption and metabolism of the filtered protein. Of further interest is the fact that the absolute rate of albumin synthesis was normal in most of the nephrotic patients, and only slightly increased in the others, regardless of serum level. It would appear from these studies, and from similar observations in protein-losing enteropathy,⁷ that the liver has a relatively limited capacity to increase albumin synthesis despite even severe depletion. This limitation, combined with variable degrees of renal excretion and breakdown of albumin, may well account for the occasionally puzzling discrepancies between hypoalbuminemia and albuminuria.

The treatment of INS is another aspect of this subject that is clouded with uncertainty. For many years pediatricians have used adrenal steroids with apparently good initial results, but it is still not settled whether these agents improve the long-range prognosis or merely induce remissions sooner than they would have occurred spontaneously with more conservative therapy. There is even more disagreement about the place of steroids (as well as other forms of immunosuppressive therapy) in the management of INS in adults. Do the benefits of these drugs outweigh the very real risks associated with their continued use? Most published experience with steroid therapy has not been adequately controlled, but at least one uncontrolled long-term study has suggested that judicious use of steroids may be helpful, particularly in patients with lipoid nephrosis or relatively minimal forms of membranous or proliferative disease.⁸

What is obviously needed to settle this vexing issue is a properly designed and controlled prospective study in which adequate numbers of patients are followed for long periods of time. As Dr. Earley and his colleagues emphasize in their staff conference, it would be essential at the onset of such a study to biopsy and classify all cases carefully on the basis of their morphologic and immunologic characteristics, for it is the general experience that those with significant membranous or proliferative lesions have a much graver prognosis than those with lipoid nephrosis.

Some years ago, a multi-center controlled trial of prednisone was initiated in Great Britain under the sponsorship of the Medical Research Council. The results after two to four years of follow-up of 125 patients have recently been reported.⁹ Although the study provides important new information, it unfortunately leaves some of the most crucial issues unresolved. In retrospect the dosage schedule employed was probably not optimal: treated patients were started on average doses of 20 to 30 mg a day for the first few weeks and then were continued on similar or slightly lower daily doses for several months. After six to twelve months of continuous therapy the dose was usually tapered, and then discontinued at two to three years in all but those with "proliferative" glomerular lesions. Doses of 20 to 30 mg a day in the initial phase of treatment may not have been quite large enough to induce remission or substantial improvement in relatively resistant cases, but when continued over long periods would be expected to cause a high incidence of complications. It is therefore not surprising that the British group found a prompt and significant improvement in proteinuria in the treated patients with "minimal" lesions (lipoid nephrosis), but insignificant and very gradual improvement in proteinuria in the other groups with "membranous" or "proliferative" lesions. They also found that the overall death rate was *higher* in the treated than in the control group, but the difference was due to a higher incidence of cardiovascular disease and steroid-related complications in the treated group. The death rate due to renal failure was conspicuously lower in the treated group, and renal function in the survivors was slightly better than among those who had not been treated.

What would be the long-term effects of steroids if used in higher initial doses, but given intermittently or for shorter periods in order to minimize steroid complications? What about the effects of other immunosuppressive agents such as azathioprine or cyclophosphamide? The answers to these questions will have to await the results of other prospective, controlled studies now being planned by cooperative groups in this country. It is to be hoped that when the results of these arduous clinical trials are finally available, we will for the first time have a rational basis for making the difficult therapeutic decisions required in the management of INS. Until

that time, nephrologists will argue and worry about this issue and will be forced to continue their reliance upon their own best judgment and the information that can be gleaned from an inconclusive literature.

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Marine Pollution and Human Health

POLLUTANTS ENTERING THE MARINE environment likely to be affecting human health fall into two major categories: microbiological pathogens, and chemical intoxicants. The microbiological constituents consist of such well-known organisms as enterobacteria, tubercle bacilli, cholera vibrios, clostridia, enteroviruses, fungi and parasites. With the few exceptions of hemophilic and obligatory parasitic bacteria, all of these microorganisms live and survive in sewage water and sea water a period of days or weeks. They also survive for a period of time when they are ingested by plankton, shellfish, or deposited on sandy beaches and on bottom sediments. Recent epidemiological studies indicate that it is justifiable to assume that a certain number of summer and autumn diseases are contracted after bathing in polluted water or spending a long time on sands in which pathogenic agents are

retained. These diseases, which include cutaneous mycoses and some bacterial infections, affect mainly children and adolescents of city origin who are normally resident far from the coasts.¹

The problem of toxicity in marine organisms from natural causes or man-produced pollutants is coming into critical focus. Aside from the mechanical and amenities aspects of pollution, in the final analysis most pollution problems are toxicological. In most instances one is concerned with the toxic effects of a chemical substance on a specific cellular system of an organism, be it plant, lower animal or man. Unfortunately some of the most serious problems facing us in the marine ecosystem today are associated with chronic intoxications that are long term and have low-level effects. The pathologic state in indicator organisms may pass undetected until it is too late to correct or control the causative pollutants. This may result in massive destruction and an enormous build-up of toxic constituents in the environment long before they are detected.

There is increasing evidence that this situation is taking place in the marine environment in many parts of the world—Southern California, San Francisco Bay, Puget Sound, New York Harbor, Baltic Sea, Irish Sea, Adriatic and Mediterranean seas and elsewhere. A large number of “naturally-occurring” marine biotoxins are now recognized. These substances are known to involve a broad phylogenetic spectrum of marine organisms ranging from protozoans to polar bears. Ingestion of these poisons can produce serious illness and death.

Since many of these biotoxins are intimately involved with the food web of these organisms, question has been raised as to the relationship of man-induced pollutants to the biogenesis of marine biotoxins. There is circumstantial evidence that biogenetic relationships may exist which may be of serious public health significance.

In addition to the naturally-occurring biotoxins, some of the most serious marine environmental problems are developing due to the man-induced intoxicants. These poisons are derived from a vast array of industrial operations, military activities, universities, shipping, hospitals, research laboratories, agricultural practices, and the like. These pollutants involve such things as heavy metals and other inorganics, oil, petro-

chemicals, a vast array of organics, and pesticides.

The build-up of highly toxic and carcinogenic substances in the marine environment in industrialized areas has reached frightening proportions. The broad spectrum of toxins and carcinogens with which man is polluting the marine environment are among the more lethal agents known to toxicologists.² There is no longer any question that these materials are entering man's marine food resources. The question is how and to what extent these poisons affect marine plants, lower animals, and human biological systems. Critical examination is urgent.

At the moment there are no adequate baselines of marine biological, chemical, and medical epidemiological data. There is a growing belief by some medical investigators that some of the chronic degenerative diseases of man may be caused by environmental intoxicants. Certainly there is a growing amount of evidence of carcinogenic, mutagenic, and teratogenic abnormalities among large populations of marine animals, fish and invertebrates, which indicate that our seas are sick. The disease of our seas will ultimately be reflected in human illness.

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The 101st Scientific Assembly

THE PROGRAM for the 101st Scientific Assembly is to be found elsewhere in this issue. It covers a variety of subjects which deeply concern most California physicians. There is an appropriate mixture of local talent and experts from afar.

While some of the scientific sections will offer their own excellent programs, several have combined to have interdisciplinary programs which should be of great interest. A number of unusual subjects will be discussed, such as the management of reading problems, aviation medicine in commercial airline operations, and wide-ranging interdisciplinary computer and educational approaches to high quality care.

There will be a stellar all-day Valentine's Day Symposium on the pressing problem of venereal disease, and the medical students on the Committee on the Role of Medicine in Society are expected to present a "happening" with audience participation on the subject "Medical Education—for Hippocrates, for the Birds, or for Practice."

Everyone should try to attend the 101st Scientific Assembly in San Francisco, February 12 to 16, 1972.

WHEN TO SEND PATIENTS TO A BURN CENTER

When should you refer a burn patient from your community hospital to a burn center?

In the hospitals I have visited where burns are treated, it appears that we can draw a line at about 30 percent, that is, burns covering about 30 percent of the body. This seems to be the point at which mortalities begin to occur more than they should in the usual surgical type of hospital. I might add that the less than 30 percent burns involving such special areas as the hands and the face, electrical burns, and respiratory burns should probably be added to that list.

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CASE REPORTS

Approach to Diagnosis and Treatment of Herpes Simplex Encephalitis

A Report of Two Cases

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ENCEPHALITIS DUE TO INFECTION with herpes simplex (*Herpesvirus hominis*) has been described as the most common cause of sporadic fatal encephalitis.¹ Herpes simplex virus was first isolated in encephalitis in 1941 from the brain of a week-old infant in whom type A intranuclear inclusion bodies were noted post-mortem.² Herpes simplex has subsequently been recognized as being frequently associated with acute necrotizing encephalitis,³ and it can present clinically as a "temporal lobe" syndrome⁴ or as an intracranial mass lesion.⁵ Improved methods of laboratory diagnosis have contributed to the early diagnosis of the clinical syndrome of herpes encephalitis. The increasing use of brain biopsy has made possible the diagnosis of

herpes encephalitis in living patients, by typical histological appearance, by specific immunofluorescence for herpes antigen, or by isolation of the virus from the biopsy specimen. A new method of making immediate serological diagnosis of herpes infection from a single specimen has also been proposed.⁶ Although cerebrospinal fluid (CSF) has proved a poor source⁷ for the isolation of herpes simplex, diagnosis by immunofluorescence for herpes simplex in CSF has been reported twice.^{8,9}

The use of iododeoxyuridine (IDUR), a thymidine analogue shown to have *in vitro* activity against herpes simplex,¹⁰ was first reported in herpes encephalitis by Breeden et al in 1966¹¹ and has been used many times since. The use of IDUR in herpes encephalitis is now accepted, although its efficacy has not been proved by controlled trial.¹ It has been felt to be efficacious by investigators evaluating it on the basis of clinical improvement and elimination of virus shedding in individual cases and by comparison of the outcome of treated cases with previous untreated cases.

The purpose of this communication is to report two additional cases of herpes encephalitis recently seen in consultation by our group. A review of herpes encephalitis suggested an improved survival in herpes simplex encephalitis treated with IDUR, as compared with previously untreated cases. On the basis of this analysis of the literature, it seemed appropriate to treat apparent herpes encephalitis with iododeoxyuridine after steps leading to specific viral diagnosis, including open brain biopsy, were begun.

Reports of Cases

Case 1. A previously healthy 22-year-old white man had sudden development of behavioral changes characterized by inability to work and failure to recognize people. He became with-

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drawn, stared into space, had visual hallucinations, and spoke in brief sentences out of context. Three weeks previously he had had a cold sore on his lip which he picked until it bled; and for one week he had had symptoms of an upper respiratory infection. On the second and third days of this illness he became febrile and had an earache, for which he received a penicillin injection. On the fifth day of illness he had a grand mal seizure and was admitted to the hospital where temperature of 40°C and nuchal rigidity were noted. Bilateral injection of tympanic membranes was observed. On neurologic examination a questionable mild right central facial paresis was noted, and Hoffmann's sign was present on the right side. Altered sensorium and behavior were observed also. The patient lay on his left side and did not respond to verbal stimuli; he did not speak except for periodic outbursts of profanity. At times he had tonic deviation of his eyes to the right, and focal temporal seizures were suspected. On lumbar puncture the CSF was cloudy with 346 white blood cells per cu mm—80 percent lymphocytes and 20 percent polymorphonuclear cells. Protein content was of 100 mg and glucose content 88 mg per 100 ml. A brain scan showed minimal findings in the left inferior frontotemporal region. An electroencephalogram showed focal slowing and spikes from the left frontotemporal electrodes. Administration of diphenylhydantoin (Dilantin®) and phenobarbital was begun but intravenous diazepam (Valium®) was necessary for control of agitated behavior. Dexamethasone also was given, 4.0 mg four times a day. On the fourth day in hospital (eight days after onset) the patient's condition suddenly deteriorated; he had right hemiparesis, a dilated unreactive pupil and unresponsiveness to deep pain stimuli. Other transient cranial nerve signs suggested impending herniation. Brain scan and left carotid arteriogram suggested a mass on its left. On craniotomy congestion and swelling of the brain was noted and there were several areas of necrosis in the left frontotemporal region. Exploration failed to reveal an abscess, and cerebral biopsy specimens were obtained. A wide decompression and grafting of the dura were performed to relieve the cerebral swelling. Microscopic sections revealed typical necrotizing encephalitis and many intranuclear inclusions.

The brain biopsy specimen was processed for

specific immunofluorescence at the California State Public Health Viral and Rickettsial Laboratory. The report that the biopsy specimen was strongly positive for herpes simplex was received the same day. On the following day (ninth day of illness) MUR was started at a dose of 100 mg per kilogram of body weight per 24 hours in a continuous intravenous infusion that was continued for five days. The patient remained comatose for 48 hours after decompression and 27 hours after MUR was started, after which time he opened his eyes, followed objects and moved all extremities; however, the right arm moved less than the left. His neck was supple, pupils were equal and reactive, and he was responsive to painful stimuli and commands. On the eighth hospital day, evidence of a cerebral salt-wasting syndrome appeared, with serum sodium of 124 mEq, serum chloride of 82 mEq and 24-hour urine sodium excretion of 439 mEq per liter. He was treated with salt and restriction of fluid.

On the tenth hospital day signs of pneumonia appeared. *Staphylococcus aureus* resistant to penicillin was recovered on deep endotracheal suction. Treatment with methicillin resulted in resolution of clinical and radiologic signs by the fourteenth day. On this day, one day after cessation of MUR, signs of bone marrow depression occurred. Maximal depression of platelets (23,000 per cu mm), hemoglobin (7.46 gm per 100 ml) and white blood cell counts (3,800 per cu mm) followed on the fourth, fifth and sixth days after cessation of MUR.

There was slow but steady improvement of neurological and mental status despite the above complications. Twelve days, 19 days and 26 days respectively after initiation of MUR therapy, the patient was able to feed himself, to walk with assistance and to speak simple words. By the twenty-sixth day neurological evaluation was negative except for mild right central facial paresis and severe receptive and expressive aphasia. Twelve months later he still had severe expressive aphasia and possible memory defect for remote learning, making a protected environment necessary.

Infection with herpes simplex was confirmed by isolation of the virus from the brain biopsy specimen. Serum specimens obtained on the sixth, twenty-fifth and fifty-first days of illness

showed conventional neutralizing antibody titers against herpes simplex of less than 1:8, 1:32, and 1:64. These same specimens showed complement-requiring neutralizing antibody titers of 1:32, 1:64, and 1:256.

Case 2. A 34-year-old white woman was admitted to the psychiatric ward of the Stanford University Hospital because of agitation, disorientation and auditory and visual hallucinations of several days' duration. Five days before admission she had had a four-day illness consisting of fever and cough, which had been treated with ampicillin. On the third hospital day mild nuchal rigidity and increased tone were noted, without focal neurological findings. The temperature was 37.5 C; other vital signs were normal. Leukocytes numbered 12,500 per cu mm of blood, with the cell differential within normal range. On lumbar puncture the opening pressure was 270 mm (water) and the CSF was clear. It contained seven leukocytes (1 polymorphonuclear) and 136 erythrocytes per cu mm, glucose 43 mg and protein 171 mg per ml. Bacterial, fungal and mycobacterial cultures, Gram-stain and India ink preparations were negative. A brain scan was normal. The electroencephalogram showed diffuse slowing. Two days later the CSF showed 120 leukocytes and 50 erythrocytes per cu mm and glucose of 30 mg per 100 ml. Blood glucose was 80 mg per 100 ml. The patient remained confused, and had right-sided movements that were interpreted as myoclonic jerks for which Dilantin® was given. The next day (seventh hospital day) she had continuous mouth and jaw movements. An EEG showed a subcortical left temporal focus. The patient was no longer responsive, this believed to be secondary to status epilepticus. Because of the low CSF glucose, administration of ampicillin, isoniazid and streptomycin was begun. On the eighth hospital day she was completely comatose. A brain biopsy specimen was obtained and decompression was carried out. Hemorrhagic inflammation was noted grossly. Histological sections showed inflammation without inclusion bodies. Immunofluorescence for Herpesvirus hominis was negative. The patient received MUR, 40 mg per kg of body weight, in a continuous intravenous infusion over the next 24 hours. On the tenth hospital day, a full supply of MUR was obtained, and she then received 100 mg per kg per 24 hours for five days.

Following the surgical procedure and during the MUR therapy, she remained completely comatose. The postoperative course was complicated by Group A streptococcal bacteremia, bilateral pulmonary infiltrates felt to be pulmonary hemorrhages, and gastrointestinal bleeding. She died of bronchopneumonia on the fortieth hospital day without ever regaining consciousness. Thrombocytopenia and leukopenia were first noted on the fourth day following the cessation of MUR therapy, and an abnormal serum glutamic oxaloacetic transaminase (SGOT) and bilirubin on the sixth day. The nadir of bone marrow depression occurred on the eighth day after cessation of MUR. At that time the platelets were 12,000 per cu mm and there was evidence of gastrointestinal and intrapulmonary bleeding. The peak abnormality in liver functions also occurred at this time, with bilirubin of 3.0 mg per 100 ml of blood. The leukocyte count was never lower than 3,800 per cu mm.

Infection with herpes simplex was suggested by a rise in complement-fixing antibody titer from 1:16 on the seventh and tenth day of illness to 1:128 on the thirty-ninth day of illness. There was also a four-fold difference in conventional neutralizing antibody (less than 1:8) and complement-requiring neutralizing antibody (1:32) on the specimen drawn on day seven. Viral cultures of the brain biopsy specimen in the Virus Diagnostic Laboratory of Stanford University Hospital after several blind passages grew a virus identified by immunofluorescence and neutralization as herpes simplex. Viral cultures of postmortem brain and lung tissue were negative and no intranuclear inclusion bodies were noted in neuropathologic examination.

Discussion

The diagnosis of herpes encephalitis can be suspected on clinical grounds. In this country, acute febrile encephalitis without an associated immunization, infectious disease or epidemiological evidence of arbovirus infection is highly suggestive of herpes encephalitis. Organic psychosis, focal neurological signs, especially those of temporal lobe origin, or signs of a mass lesion are typical of herpes encephalitis. Often the presence of a mass lesion is demonstrated preoperatively, as in our first patient, by angiography or brain scan.

TABLE 1.—Mortality of "Untreated" Herpes Encephalitis

Reference	Overall mortality		Comatose patients		Non-comatose patients	
Drachman et al (4)	3/6	(50%)	1/2	(50%)	1/6	(17%)
Lieder et al (15)	4/15	(27%)	3/9	(33%)	2/4	(50%)
Miller et al (16)	10/20	(50%)	10/13	(77%)	0/7	(0%)
Olson et al (7)	25/36	(70%)	24/30	(80%)	1/6	(17%)
Nolan et al (13)	3/7	(43%)	3/4	(75%)	0/3	(0%)
Meyer et al (17)	5/13	(38%)	—		—	
Miller, Ross (18)	5/11	(46%)	—		—	
	55/108	(51%)	41/58	(71%)	4/26	(15%)

Herpes encephalitis, when suspected, may rapidly be confirmed in some cases by brain biopsy. When positive, specific immunofluorescence showing the presence of the herpes antigen in brain tissue can confirm the diagnosis the day of the biopsy, as in our first patient and one other reported patient¹², though the frequency of false negatives by immunofluorescence, as occurred in our second case, is not yet known. The finding of intranuclear inclusion bodies in a brain biopsy can also yield an immediate presumptive diagnosis. However, intranuclear inclusions are frequently absent. For example, in five patients with serological evidence of herpes encephalitis, Nolan et al found inclusions in only one of the five biopsy specimens.¹³ Finally, rapid diagnosis of herpes encephalitis might be made by finding herpes-like particles in electron micrographs of touch preparations of the brain biopsy. Such preparations could be made the same day, and have been reported to be of value in other viral syndromes.¹⁴

Isolation of the virus from CSF or brain biopsy specimens permits definitive diagnosis, but several days may be required for the virus to be detected in tissue culture. Serological confirmation of herpes infection by a fourfold rise in either neutralizing or complement-fixing antibody may not always be noted and is rarely useful in acute situations. Frequently the patient already has a high-titer of antibody when first seen, precluding the detection of an antibody rise. Recently, Lerner et al reported that the diagnosis of herpes infection could be made from a single serum specimen, by the finding of fourfold higher levels of complement-requiring neu-

tralizing antibody compared with conventional neutralizing antibody,⁶ but this has not yet been confirmed by other investigators. Even this method has an inherent delay of 24 to 36 hours.

The diagnosis of herpes encephalitis in both of our patients was suspected on clinical grounds. Open brain biopsy helped establish the diagnosis within 12 hours in one patient by means of positive immunofluorescence. In the other patient, open brain biopsy was immediately helpful only in that it helped rule out other infectious causes of encephalitis. In both cases, serological rise in complement fixing antibody helped confirm infection with herpes simplex, as did viral isolation. Isolation of the virus in the second case, however, required several blind passages. Herpes simplex was not isolated from a part of the same specimen that was sent to the State Laboratory, suggesting an advantage of having available a hospital based viral diagnostic laboratory where cultures can be pursued with clinical insights. The initial serum specimens taken on the sixth day of illness (Case 1) and on the seventh day of illness (Case 2) were suggestive of herpes simplex infection by the ratio of complement-requiring to conventional neutralizing antibodies.

Data on mortality and incidence of permanent neurologic sequelae following untreated herpes encephalitis vary^{4,7,13,15-18} (Table 1). There are also many individual case reports of fatal cases, though Pierce et al reported two severe cases with survival, and MacCallum one case.^{5,19} The overall mortality of untreated herpes encephalitis in the seven reports summarized in Table 1 was 51 percent (55 of 108) and the range was

from 27 percent to 70 percent. The mortality for patients with coma was 71 percent (41 of 58), compared with only 15 percent (4 of 26) for those who did not have coma. Since five of the seven reported series^{7,13,15-18} deal with retrospective analysis of cases searched out by a central reference laboratory, the patients had been treated in diverse hospitals. The method of diagnosis of herpes infection varied widely, being based in some cases only on a rise in antibody titer, although most of the fatal cases were confirmed by isolation of the virus at postmortem examination.

The possibility of using *MDR* in the treatment of herpes encephalitis was suggested by the *in vitro* finding that *MDR* inhibits a variety of DNA viruses, including herpes simplex, most likely acting as a thymidine analogue and interfering with the synthesis of viral DNA.¹⁰ Experimental animal and clinical data confirmed its efficacy in keratitis due to herpes simplex,²⁰ and it has become an accepted mode of therapy for this condition. *MDR* was first used systematically in compromised hosts with severe disseminated vaccinia and varicella-zoster infections.¹⁰ Its use in systemic infection with cytomegalovirus (CMV) has also been reported.²¹ Its use has also been reported in an immunosuppressed patient who received the drug locally and systemically, without apparent benefit, for widespread ulcerating cutaneous and mucosal herpetic lesions.²²

We have attempted to summarize all the published cases of *MDR*-treated herpes encephalitis, excluding only neonatal infections (Table 2).^{11-13,23-29} The overall mortality among the *MDR*-treated patients with coma was 29 percent (5 of 17), while one of three patients without coma died. Seven of the 14 surviving patients made full recovery, while the rest were left with moderate or severe neurological deficits. The 29 percent mortality observed in the *MDR*-treated patients with coma compares favorably with the 54 percent overall mortality and 71 percent mortality of comatose patients observed in the symptomatically treated group.

Herpes encephalitis in newborn infants, particularly prematures, is often a disseminated infection, rather than only encephalitis as in adults, involving the skin and many viscera as well as the CNS, and it carries perhaps an even worse prognosis. It is almost always owing to primary infection, acquired either transplacentally or at

the time of delivery.³⁰ It may more often be due to herpes simplex type II, which has been said to be more resistant to *MDR*. Cases of neonatal herpes infection treated with *MDR* have been grouped separately (Table 3).^{9,31-33} Only two of seven patients died, though a third died six months later of pneumonia. However, only one of these seven patients was felt to be "normal" following recovery from the infection. One patient was treated twice—he improved following *MDR* therapy on the tenth day of illness, but then had a clinical and virological relapse, with herpes again found in the CSF. He was again treated with *MDR*, and then the virus was successfully eradicated, though he had evidence of hydranencephaly at age 12 months.⁹

The efficacy of *MDR* in herpes encephalitis is suggested both by the lowered mortality found when the treated cases, as a whole, are compared with the previously published experience, and by the course of the illness described in many of the cases, wherein improvement seemed temporally related to the use of *MDR*. In a disease such as viral encephalitis, one would expect that early treatment might be much more likely to bring benefit than treatment initiated late in the disease, where damage to brain cells caused both by viral replication and brain swelling is likely to be permanent. A trend favoring earlier treatment is not, however, apparent from the summarized data in Table 2, suggesting either that treatment may not have affected outcome, or that the more indolent cases, diagnosed and treated later in the course of disease, have a better prognosis. Although the improved outcome in the *MDR*-treated cases suggests that *MDR* may have been of benefit in herpes encephalitis, there are many other factors that might account for this difference in outcome. "Symptomatic" care of encephalitis may have been quite different in one medical center than in another, and may have improved overall in the time period when *MDR* was used. Surgical decompression procedures may have been more common among the *MDR*-treated cases, possibly because of increased recognition of herpes encephalitis as causing a mass lesion, or because of more vigorous attempts to make a specific diagnosis.

Most patients have had signs of toxicity related to *MDR*, including jaundice, other liver function abnormalities, bone marrow depression, stomatitis, and alopecia. Bone marrow depression oc-

TABLE 2.—Summary of Reported IDUR-Treated Cases of Herpes Encephalitis

Author and reference	Age (yr)	Sex	Coma present (HD)*	Mass lesion present	Focal started Neuro-logical signs	IDUR Dosage			Side effects	Surgical decompression or biopsy (HD)	Outcome	Means by which diagnosis established
						Day after first symptom	HD begun	Total dose mg/kg				
Breden et al (11) [Page et al (23)]	34	M	+(7)	+Art +Scan +EEG	+	10	8	550	↓ WBC ↓ RBC ↓ Platelets Stomatitis Abnormal liver function tests	Bx 5 7 8	Recovery Minimal neurological signs	Isolation (Bx) Serology (Neut)
Buckley, MacCullum (24)	41	F	—	—Art —PEG —EEG	+	21	5	14	None	2	Quadriparetic, dysphasic	Isolation (Bx) Serology (Neut, CF)
Evans et al (25)	8	F	+(5)	+EEG	+	55	53	500	None	53	Hemiplegic Mental retardation	Isolation (Bx) Serology (CF)
Marshall (8)	13	M	+(10)	+EEG +Art	+	10	10	200	↓ WBC	8 10	Recovery Minimal neurological signs	Fluorescent Ab on CSF, venous blood Isolation (Bx) Serology (CF)
Bellanti et al (26)	1	F	+(1)	+EEG	—	13	13	600	Abnormal liver function tests Hepatomegaly	5 20	Recovery Moderate spasticity	Isolation (Bx) Serology (CF)
Dayan, Lewis (27)	60	M	+	?	+	?	?	?	Cholestatic jaundice	5	Died	Isolation (Bx)
Silk, Roome (12)	6	M	+(4)	?	+	6	6	550	Abnormal liver function tests Alopecia	Bx	Aphasic, hemiplegic, incontinent, retarded	Immunofluorescence (Bx) Isolation (Bx) Serology (CF) Serology (CF)
Nolan et al (13) [Meyer et al (28)]	57	F	+(4)	+EEG —Art	+	13	10	430	(died)	Bx	Died	Isolation (Bx, PM) Inclusion bodies (Bx, PM) Serology (CF, Neut, CF-neut) Serology (CF, Neut, CF-neut)
	24	F	+(6)	+EEG —Art	+	13	6	430	Stomatitis ↓ WBC ↓ RBC ↓ Platelets Alopecia	—	Recovered	Serology (CF, Neut, CF-neut) Serology (CF, Neut, CF-neut)
	22	F	—	+Scan —EEG	—	14	6	430	Stomatitis ↓ WBC	—	Recovered	Serology (CF, Neut, CF-neut)

16	F	+	(1)	+	EEG	-	3	?	450	Stomatitis ↓ WBC ↓ Platelets Alopecia	Bx	Recovered	Serology (CF, Neut, CF-Neut)
62	F	-		+	-Art +EEG	+	6	3	100	(died)	Bx	Died	Isolation (Bx, Pm) Serology (CF, Neut)
Rappel et al (29)													
58	M	+		+	+EEG +Art -Scan	+	16	?	500	"Transient hepatic toxicity and bone marrow depression"	9	Died	Isolation (Bx) Serology (CF) Inclusions (Bx, PM) Serology (CF)
12	F	+		+	+EEG +Art	+	16	?	320	None	16	Recovered	
56	M	+		+	+EEG	-	27	?	500	"Transient....." Alopecia	27	Recovered, impaired mental capacity	Serology (CF)
45	F	+		+	+EEG +Art +Scan +PEG	+	18	?	500	"Transient....."	-	Recovered Moderate memory defect Slight aphasia	Serology (CF)
65	F	+		+	+EEG +PEG -Art	+	9	5	500	"Transient....."	9	Died	Electron microscopy
Our patients													
22	M	+	(8)	+	+EEG +Scan +Art	+	9	5	500	↓ WBC ↓ Platelets ↓ RBC	8	Aphasia	Immunofluorescence (Bx) Isolation (Bx) Serology (Neut, CF-Neut) Serology (CF, CF-Neut) Isolation (Bx)
35	F	+	(4)	+	+EEG -Scan	-	6	6	500	↓ WBC ↓ Platelets ↓ RBC ↑ SGOT ↑ Bilirubin	6	Died	
TOTALS:													
1-65 yr	F-12 M-8	17/20	15/18 5/7 5/11 2/4	+EEG +Scan +Art +PEG	15/20 6-55 days	15/20	6-55 days	320-500	5/18 Stomatitis 12/18 Bone marrow depression 9/18 Abnormal liver function tests 6/18 Alopecia	17/20 Bx and/ or decompression	6/20 Died 7/20 Recovery, moderate or severe residua	12/20 Isolation 18/20 Serology 3/20 Immunofluorescence 1/20	Electron microscopy

NOTES: *HD = Hospital Day
Art. = Carotid Arteriogram
Scan = Radioactive brain scan
PEG = Pneumoencephalogram
Bx = Biopsy
PM = Post-mortem

CF = Complement fixing antibody
Neut = Neutralizing antibody
CF-Neut = Ratio of complement-fixing
neutralizing antibody to
conventional neutralizing
antibody

TABLE 3.—Summary of Reported IDUR-Treated Cases of Herpes Encephalitis in Neonates

Reference	Age,* Sex	Total Dose IDUR	Other Organ Involvement	Side effects	Outcome	Means by which diagnosis established
Partridge, Millis (31)	4 days, FT, ** F	580 mg/kg	Skin ? Heart ? Lungs	None	Died. (Improved following IDUR, but relapsed 5 days later)	Isolation (vesicles, nose and throat swabs)
Golden et al (9)	4 days, P, *** M	1000 mg/kg (two 500 mg/kg courses, 23 days apart)	Eyes Skin	WBC Platelets RBC	Retarded. (Improved following first course of treatment, but relapsed with virus re-isolated from CSF)	Isolation (CSF, vesicles, throat swabs) Immunofluorescence (CSF)
Tuffli, Nahmias (32)	7 days, P, F 14 days, P, M	200 mg/kg 250 mg/kg	Eyes Skin Skin	WBC "Aphthous stomatitis"	Retarded. Died age 6 months Well, recurrent herpes infection	Isolation (HVV II)*** (vesicle, eyes, throat) Isolation (HVV II) (Skin) serology
AJN (reported in Reference 32)	Infant, P	200 mg/kg	Skin Viscera	? ?	Died Mild hemiparesis	Isolation (HVV II) (brain, liver) ?
Wenzel (reported in Reference 32)	3-month infant	250 mg/kg 10 mg/kg intrathecally	?	?		
Charnock, Cramblett (33)	11 day, FT, F	410 mg/kg	Skin	Platelets	Impaired	Isolation (skin, brain bx)

NOTES: * Age when first evidence of herpes infection appeared
 ** FT = Full term
 *** P = Premature
 **** HVH II = *Herpesvirus hominis* Type II

curs usually after cessation of therapy, and it may be severe, as it was in our second case where the resultant thrombocytopenia was considered responsible for the pulmonary and gastrointestinal hemorrhages that complicated the post-treatment course.

The establishment of the efficacy of IDUR in herpes encephalitis by means of controlled trials seems mandatory before IDUR therapy can be considered generally accepted for this condition. The premature acceptance of IDUR would commit to treatment patients with herpes encephalitis in spite of the potentially serious toxicity associated with this agent, and it also might preclude the experimental use of other (possibly more effective) antiviral drugs. The fact that not enough cases of herpes encephalitis are seen at any one center to permit any kind of valid controlled trial has been recognized. A large double-blind trial, involving eight to twelve medical centers is currently being planned.

There are other situations in which systemic IDUR has been and can be used. Severe life-threatening local and disseminated herpes infection has been noted in a variety of "compromised" hosts; in premature infants, patients with gross malnutrition, severe burns or eczema, immunosuppressed transplant recipients or patients with cellular immune defects.³⁴ All such infected patients are also potential candidates for antiviral therapy. Furthermore, immunosuppressed patients and patients with leukemia or lymphomas are also known to have a higher incidence of severe infections with other DNA viruses such as varicella-zoster, cytomegalovirus, and vaccinia. Such patients have also been treated in the past with IDUR or other thymidine analogues, cytosine arabinoside, isatin-B-methylthiosemicarbazone, and polycytidylic-inosinic acid, an interferon inducer.³⁵ If the use of these antiviral drugs is going to be considered, it would seem important that they be used as early as possible in the course of the severe viral infection, rather than as a desperation measure in an already dying patient. Early diagnosis and specific treatment will require (1) an awareness of the clinical syndromes produced by these viruses. (2) a willingness to use aggressive means of diagnosis as soon as a life-threatening viral infection is suspected, such as brain biopsy in suspected herpes encephalitis and liver or lung biopsy in suspected CMV infections, and (3) a rapid, even if provisional,

means of specific diagnosis, including immunofluorescence and electron micrography of such biopsy material.

Summary

Because of our analysis of reported cases of herpes encephalitis, it appeared appropriate to treat two patients with herpes simplex encephalitis with iododeoxyuridine, after appropriate diagnostic steps were begun. Diagnosis was established with open brain biopsy in one patient within 12 hours, by means of specific immunofluorescence, whereas in the other patient immunofluorescent study of biopsy material was negative and the virus was only demonstrated after several blind passages of biopsy material. This report is presented to illustrate our approach to specific diagnosis and attempted treatment of significant virus infection in man.

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Treatment with Human Growth Hormone (Li) for Over Eight Years – Effects of Long-Term Therapy in a Pituitary Dwarf

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TRIALS OF HUMAN GROWTH hormone (HGH) published to date¹⁻¹² have generally reported that this hormone is effective in increasing the rate of growth in pituitary dwarfism. However, to be of fullest benefit to the patient, treatment should be continued for a period of years, usually until skeletal maturity makes further use of the hormone ineffective. In patients receiving long-term therapy there is usually a diminishing rate of growth after the first year, and occasional resistance to the hormone has been reported. In some cases antibodies to HGH have been demonstrated and have been considered a factor in this resistance.^{6,10,13} Soyka et al.¹² recently were able to find in the literature reports of 18 patients who had received treatment for more than two years. The longest period in this group was 6.13 years of interrupted therapy, reported by Prader et al.¹⁰

The present report is on a patient who received treatment from the early days of our investigation with this hormone, and who continued to respond over a period of more than eight years. It

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is of interest that modified beef growth hormone (alpha core)¹⁴ was tried early in the course of treatment.

Report of a Case

The patient was first seen 11 April 1958 at the age of ten years, one month. Family heights were: Father, 5 feet 9 inches; mother (deceased) "normal"; two half-brothers, aged three and a half and six years, "normal." The patient's size had been normal until age 3, when his skull was fractured and he was comatose for eight days. Left optic atrophy then developed, and diminished vision on that side still persisted. Growth had been very slow since the accident, and his height when examined was 44½ inches, or 112.2 cm (average for age, 55 inches or 139.7 cm). Body proportions were normal and genitalia were small normal for build. Bone age (hand and wrist) was four years six months, and from multiple centers five years. Initial treatment was with thyroid and methyltestosterone for two and a half months and the patient's height increased to 44½ inches (114 cm) in that time.

The first admission to University of California Moffitt Hospital was 28 July 1958. The patient's age was ten years four months, height 45 inches (114.5 cm) and bone age (hand and wrist) six years. An x-ray film of the skull was normal. Laboratory studies showed:

Urinary 17-ketosteroids 1.9 mg in 24 hours

Urinary 17-hydroxycorticoids 4.7 mg in 24 hours

Urinary follicle stimulating hormone (mouse uterine method) negative at 5 units

Protein-bound iodine 5.6 micrograms per 100 ml

Iodine¹³¹ uptake 18 percent in 24 hours; increased to 29 percent after administration of thyroid stimulating hormone (TSH)

Glucose tolerance test: fasting, 65 mg per 100 ml; 1 hour postglucose 110 mg per 100 ml, at 2 hours 117 mg, at 3 hours 98 mg and at 4 hours 96 mg

The diagnosis was hypopituitarism secondary to trauma.

Balance studies with human growth hormone* showed definite nitrogen retention. Modified beef

*The human growth hormone was prepared in the Hormone Research Laboratory of this University, under the direction of Dr. C. H. Li, using his method.^{15,16} Sterilization was accomplished by passing the solution through a B-D Swinny filter adapter, using a millipore filter type HA 0.45 μ .

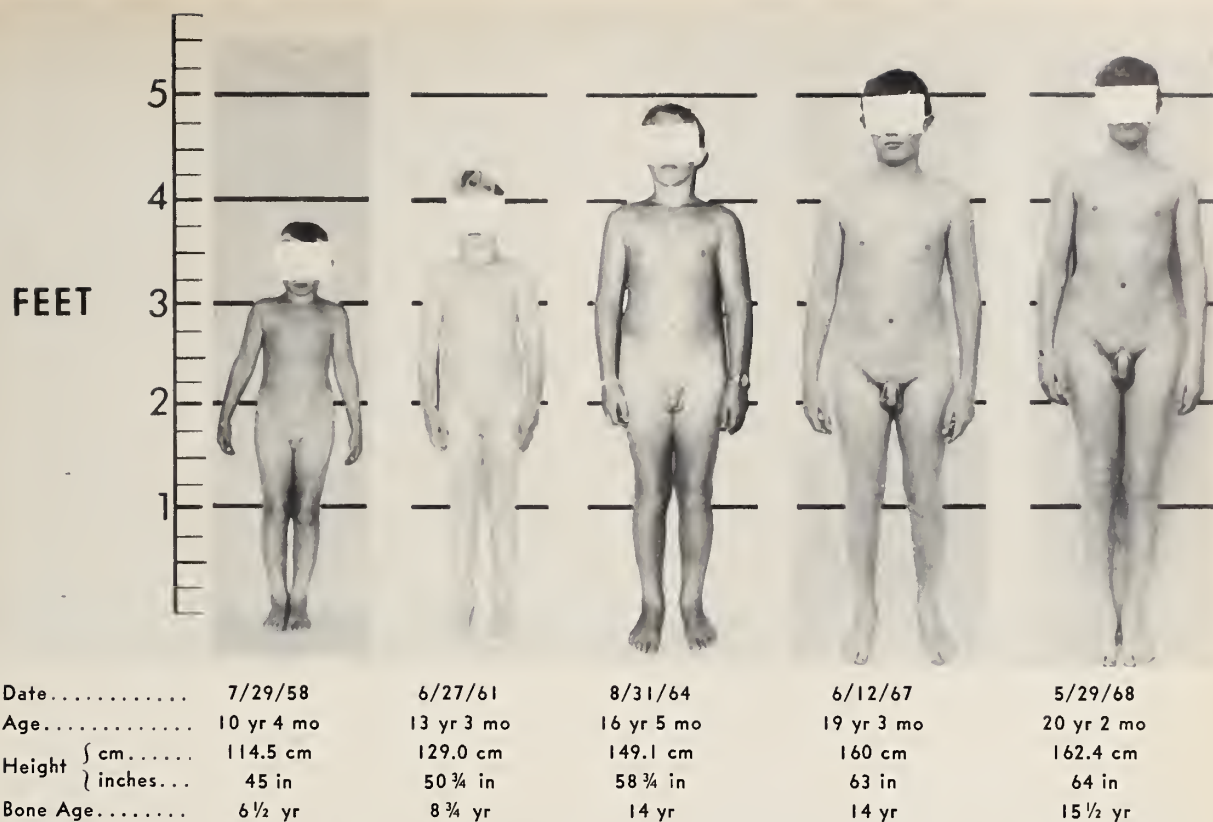


Figure 1.—Appearance of the patient before and during treatment. The four frames beginning at the left were taken at intervals of approximately three years. The frame at the right shows the appearance at end of treatment.

growth hormone (alpha core)¹⁴ also was tried with variable results. A small amount of nitrogen retention occurred following the HGH trials, but later attempts were equivocal or negative.

A trial of therapy with the alpha core beef hormone was given for five months. On a dose of 10 to 20 mg daily intramuscularly, no growth resulted. A small dose of HGH (5 mg once weekly) was added and the patient grew three-eighths of an inch (1 cm) in three and a half months. The alpha core beef hormone was then stopped and HGH was continued, with growth going on at the same rate.

Therapy with HGH was then continued as indicated in Chart 1. Dosage was adjusted to response and on 19 October 1959 was increased to 5 mg twice weekly and later three times weekly. Control periods of six months (13 December 1960 to 27 June 1961) and five months (11 July 1962 to 27 December 1962) were included in the plan, and during those periods the rate of growth de-

creased. On 10 April 1963, sodium l-thyroxine 0.2 mg daily, was added to the regime (butanol-extractable iodine had been 2.6 micrograms per 100 ml). Bone age was checked periodically as indicated in Chart 1. Laboratory values also were checked at intervals, with results as discussed below. Sexual maturity started with erections at age 14, and some pubic hair was present at age 15. When the patient's age was 18 years 9 months fluoxymesterone, 2 mg daily, was added to the routine. At this time the patient had moved away from this area and also was away from home in college most of the year. He admitted being lax about taking injections and oral medications. Sex function was reported as normal, although no axillary hair was present and his voice was of pre-puberal pitch. His final visit was on 29 May 1968, when he was 20 years and 2 months of age. At that time he was 63 3/4 inches tall (162.4 cm) and the bone age was read as 15 1/2 years from the hand and wrist and 16 1/2 years from multiple centers

LINEAR GROWTH RESPONSE TO HUMAN GROWTH HORMONE IN PITUITARY INFANTILISM

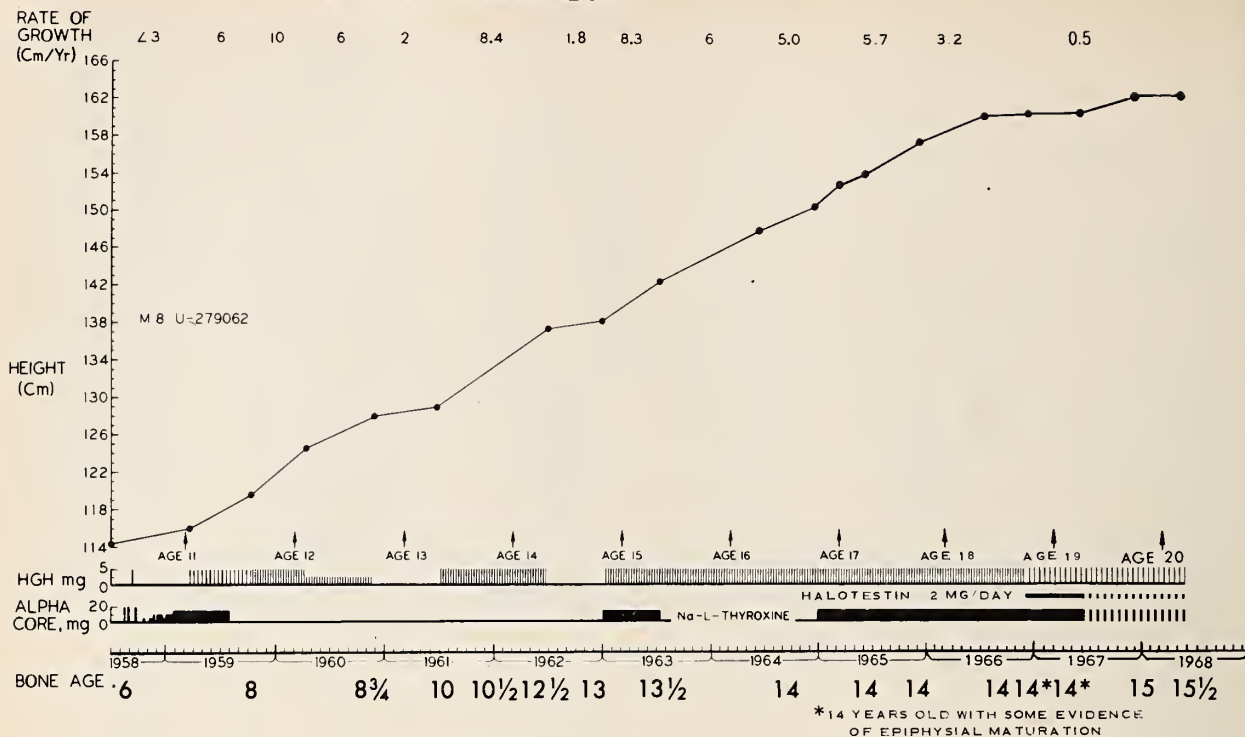


Chart 1.—Growth curve of patient during treatment. Rate of growth and types of treatment are indicated. Note flattening of curve during control periods at age 13 and 14. Also note increase in rate of growth with addition of thyroxine to regime at ages 15 and 16¾ years.

(Dr. A. Justin Williams). HGH was discontinued and the patient was advised to continue thyroxine and fluoxymesterone for one more year.

Discussion

In this case, HGH was first administered for balance studies on 1 August 1958, but regular injections were not started until 5 March 1959. They were continued except for control periods until 27 December 1967, a total of eight years nine and a half months. The patient continued to respond during the time of treatment with a total growth of 18¾ inches (47.9 cm). Irregular treatment for an additional five months produced no further growth. Final height at age 20 was within the normal range for adult males.

Short trials with other methods of stimulating growth were of some interest. Thyroid and methyltestosterone resulted in ¾ inch (2 cm) of growth in two and a half months, but modified beef growth hormone (alpha core) had no apparent beneficial effect.

The rate of growth, calculated in cm per year,

increased from less than 3 to a peak of 10 on HGH therapy. It gradually decreased after 1963, but the addition of sodium l-thyroxine to the routine resulted in some recovery for a time. Later fluoxymesterone, 2 mg daily, was added. This dose usually has good anabolic effect without increasing the rate of bone maturity, and also has some effect on genital development.

However there was a gradual slowing of response, as has been noted by many investigators. Tests for growth hormone antibodies were carried out after six and seven years of treatment and none were detected.* It is our impression that after interruption of HGH treatment during control periods there is usually a lessened response.

Bone age tended to approach the chronological age from ages 13 to 15 but then the maturity slowed and was not influenced by the addition of sodium l-thyroxine. Interpretations shown in Chart 1 were all from the hand and wrist. It seems obvious that although estimations of bone

*Performed by Dr. Mary L. Parker of St. Louis and Dr. John Linfoot of Berkeley.

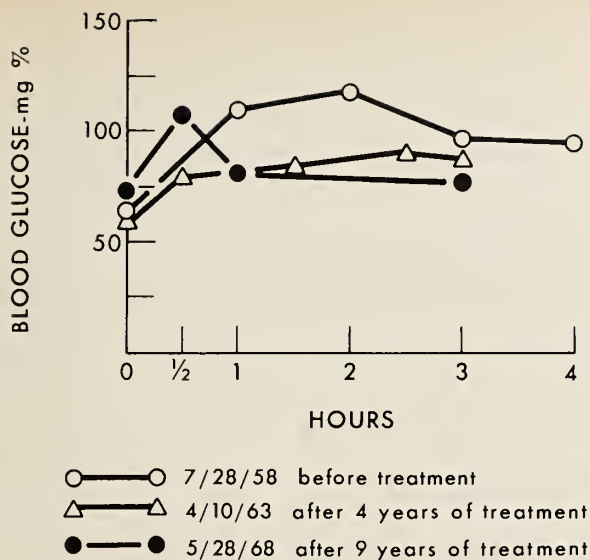


Chart 2.—Glucose tolerance curves before and during treatment. No evidence of diabetogenic effect from therapy.

age are of interest and are a useful guide, they remain only grossly accurate. However the conclusion seems warranted that treatment with HGH did not cause undue increase of rate of bone maturity in this patient.

Serum growth hormone measurements were all low, being less than 0.5 nanograms per ml at ages 17 and 18, and 1.5 nanograms per ml at 19. With an insulin tolerance test growth hormone levels were 1.0 nanograms per ml at 30 minutes, 0.5 at 1 hour and 0.65 at 2 hours. These values would indicate that the growth hormone reserve was close to zero, and were consistent with the diagnosis of growth-hormone deficient dwarfism.

FSH excretion in the urine was variable as measured by the mouse uterine weight test. It was negative at 5 units at first and periodically thereafter; but at ages 13 and 15 positive tests were reported at 20 units, and at 16 a single test was reported as positive at 80 units. This test is subject to some laboratory variation, but the results seemed to indicate intermittent release of gonadotropins from the pituitary between the ages of 13 and 18 years.

Adrenal function measurements generally were low; urinary 17-hydroxycorticoids were 4.7, 2.7, 1.7, 4.6, and 2.4 mg in 24 hours at various times. Urinary 17-ketosteroids in the same specimens of urine were 1.9, 0.6, 0.5, 0 and 1.2 mg in 24 hours. Stimulation with 25 units of ACTH intravenously

for eight hours on three successive days at age 19 resulted in a rise in 17-hydroxycorticoids from 4.6 to 33.3 mg in 24 hours and in 17-ketosteroids from 0 to 3.7 mg. When metyrapone, 30 mg per kg of body weight was administered at age 15, 17-ketosteroids rose from 3.8 to 5.1 mg in 24 hours, indicating a somewhat diminished pituitary response. A Medic-Alert disc indicating possible need for cortisone therapy in the presence of unusual stress was provided for the patient.

Glucose tolerance in this patient was not affected by the prolonged use of HGH (Chart 2). No other side effects were noted.

This experience would seem to indicate that if HGH is available for a long enough period, growth to within the normal range of adult height can be achieved in a pituitary dwarf.

Summary

A male pituitary dwarf was first given HGH at age ten years four months. Regular treatment with HGH was started at age 11 and continued except for two control periods until age 20 years 2 months. Response had continued until age 19 years and 9 months. During this period of eight years nine and a half months, the patient grew 18½ inches (47.9 cm) to a height of 63½ inches (162.4 cm) which is within the normal range for adult males. The rate of growth reached a peak of 10 cm a year, but later gradually slowed, though it was increased at age 15 by the addition of sodium l-thyroxine to the regime. Bone age was seven and a half years at the start of therapy and gradually approached chronological age during treatment, reaching 14 at age 16; but then the rate of maturity slowed and it was 15½ at age 20. A trial of modified beef growth hormone (alpha core) early in the study did not stimulate rate of growth. No side effects were observed during treatment.

ACKNOWLEDGEMENT: During the years of this patient's treatment, Dr. William C. Deamer, Dr. John J. Hutchings, Dr. Lola L. Van Campemolle, Dr. F. Stanford Massie, Dr. Ned J. Whitcomb and Dr. Stanley Galant participated in his hospital management and care.

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MENSTRUAL CRAMPS IN TEENAGERS

Menstrual cramps in the teenager are often the cause of unnecessary anxiety. Many a mother, forgetting what her own puberty was like, comes to you with great concern because her daughter who has menstruated uneventfully for a year or two without any pain suddenly begins to have cramps. The implication is that she must have contracted some dire disease. Occasionally, this is in fact true—it may be one of the rare instances of endometriosis. But 98 percent of the time she has simply matured enough to begin to ovulate. This is therefore an indication of the fact that she is maturing and she probably will be fertile. I think in dealing with these patients it's very important to always do a bimanual examination because, in the occasional case, there is an indication for culdoscopy and for a vigorous search to demonstrate endometriosis. That bimanual examination will have enormous reassurance value for the patient, too.

The management of these cases can follow one of two lines. In girls who do not have severe pain, simple analgesics are very effective. I encourage these girls to buy a pill box and carry some preparation like Edrisal.[®] When their period begins, they should take two of these every two hours—without waiting for the cramps to actually start. . . .

This simple regimen is obviously not going to work for girls with severe cramps, dizziness, faintness, and vomiting. They have got to have either one of these analgesics fortified with codeine or prevention of cramps by some kind of estrogen and progesterone regimen to inhibit ovulation and abort the cramps. I don't like to put oral contraceptives into the hands of these girls. Therefore I like to tailor-make a program—using something like Premarin[®] and Pranone[®] or Norlutin.[®] Some of my colleagues like to reserve this suppression of ovulation for great occasions only, like high school graduation and the senior ball. I tend to be more permissive than that. In girls who are having scholastic problems, who are missing one or two days of school a month, I like to do this during the school year and then stop during the summer and see if analgesics will work better—and usually they will.

So a strong dose of reassurance with the word that when the girl does marry and become pregnant, she will be cured of her cramps, that this is simply an interim treatment, this is usually all that is required.

—JANET W. McARTHUR, M.D., Boston
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Fingernail Furrows (Beau's Lines) As a Retrospective Index of the Severity Of Asian Flu in 1968-69

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THE SENSITIVITY OF THE NAIL beds to systemic illness was first reported in 1846, when Beau¹ observed transverse furrows of the nails following fever. Wilks² in 1888 reported a similar effect from the stress of seasickness and diarrhea. Since then several reports³⁻⁶ have described the effects of various systemic conditions, febrile, metabolic and emotional, in producing Beau's lines. The furrows appear from under the nail-fold about a month after acute illness and grow forward until they are cut off five or six months later. From the position of the furrow, one can calculate with reasonable accuracy how long ago the illness occurred. The average daily growth rate of nails of adults is said to be 0.104 to 0.108 mm a day.⁴

Reports are numerous on Beau's lines following bacterial infections but few on the concomitance of virus infections and the occurrence of this physical sign. Sibinga⁴ found pronounced slowing of nail growth in 23 patients during infection with measles, but he did not indicate whether or not Beau's lines developed later. William Bean,^{7,8} in his classical study of his own nail growth pattern over a 20-year period, noted a decided decrease in nail growth rate during an episode of mumps. He found no effect from "occasional bouts" of "influenza," colds,

and other illnesses. Except for the reports of Sibinga and of Bean, we have been unable to find references to the development of Beau's lines following classical influenza or other viral diseases. The present note appears to be the first report associating Beau's lines and influenza.

The 1968-69 epidemic of the A₂ Hong Kong variant of Asian flu was characterized by clinical severity and excessive mortality in the United States. One of the authors (NLP), then at age 46, had suffered a severe illness of clinically typical influenza, accompanied by severe constitutional symptoms and fever lasting eight days. About two months later distinct Beau's lines were noticed in the middle of all his fingernails on both hands and were attributed to the episode of influenza. (See Figure 1.)

Because of the then prevalent pandemic, we believed it worthwhile to determine the frequency of Beau's lines in others who had had influenza severe enough to remain away from work several days or more. Accordingly, all persons who attended the University of California Medical Center Employees Clinic during February and March 1969 were asked whether they had been ill from a disease clinically characteristic of influenza during the previous three months and, if so, to indicate the duration and severity of their illness. A diagnosis of influenza was considered as probable if the employee reported having had an illness characterized by relatively abrupt onset, chills, fever, malaise,

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Figure 1.—Transverse furrow (Beau's line) in the middle of the thumb nail about two months after bout of illness typical of severe influenza.

muscular aching, cough, coryza, headache and severe prostration. No attempt was made to isolate the etiologic virus or to demonstrate specific antibody. We examined for nail-bed furrows all those responding affirmatively.

Of 21 employees who reportedly had had severe episodes of influenza for a week or longer, seven (33 percent) had Beau's lines on the nails of both hands. Six additional employees reported less severe influenza-like illnesses of less than six days. They and 35 other employees reporting to the clinic for a variety of reasons and who did not have influenza during this period had no nail furrows. These data suggest

that the growth of the nail bed was impaired to a significant degree in many persons who had severe influenza during the pandemic of 1968-69.

The mechanism leading to the arrest of nail growth during acute systemic illness is not known. The fingernails are continuously-growing structures and might be expected to show impairment of growth under various pathophysiologic conditions. Sibinga⁴ documented the effect of fever in suppressing nail growth, but in view of recent evidence indicating that chromosomes may be severely damaged by viruses,^{9,10} a possibility to be considered is that the influenza virus directly affects the mitotic mechanism of the continuously active germinal cells of the nail bed. In future epidemics of influenza and other viral diseases, it would be of interest to make careful studies of nail growth, as well as of other systems which undergo continuous growth and differentiation throughout life, with attention to nutritional status, genetic and racial differences, and correlations with the degree and specificity of antibody response.

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EXAMINATION OF SALIVA IN SALIVARY GLAND DISEASE

In diagnosing salivary gland disease, it's very important to check the character of the saliva. Microscopic examination can be rewarding.

For example, one of the only ways to diagnose recurrent allergic parotitis (with periods of complete lack of symptoms between episodes) is the presence of eosinophils in the saliva. It's very simple to do, just capture a drop, put it on a slide, air-dry it, and stain it, as you would a nasal smear.

—BRIAN F. McCABE, M.D., Iowa City
Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 4, No. 4, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057

"Heal Yourself"

GERALD BESSON, M.D., *Sunnyvale*

EDITOR'S NOTE: *"Heal Yourself"* is a report of the Citizens Board of Inquiry into Health Services for Americans which seems to be destined for fairly wide dissemination. The approach is familiar and the findings deal harshly with health care in this nation. This report is unusual in that it carries with it an articulate "Dissenting Opinion" by Gerald Besson, M.D., of Sunnyvale who was an active and participating member of the Board. Because they believe his dissent is of broader interest than just this report, the editors have asked Dr. Besson to prepare an introductory statement summarizing the report to be published along with his dissent. Both Dr. Besson's "Introductory Statement" and his "Dissenting Opinion" are presented herewith.

—MSMW

Introductory Statement

It has become quite fashionable these days to be critical of many shortcomings in our society. Indeed, this revolution in societal values, the questioning of meaning, purpose and quality of our lives represents a true discontinuity in civilization's progress and augurs well for our future. At the same time, there is a danger in the frequent lack of discernment between the good and the bad in our social institutions. All too often, critics overstate their case and imply that the only way to correct social inequities is to tear down the old and start anew with a clean slate. Besides the impossibility of implementing changes in that fashion, at least in our democratic society, there is a growing hazard to much that is of great value in our social institutions from the

increasing acceptance of this approach. All too often what passes as conventional wisdom is merely repetition of uncritically accepted conclusions that are said to reflect public demand. Such demand then may stridently press for something, anything different from the old. And so it is with medicine.

Two years ago, the author was asked to serve on a Citizens Board of Inquiry into Health Services for Americans. The Board was created to focus attention on the consumers' perceptions of unmet needs in health services. It purported to bring attention to the consumers' story by interviewing users of health services in various parts of the country. It also interviewed providers and third party representatives. Out of these interviews developed a report published earlier this year entitled "Heal Yourself." * The report in its entirety should be read for a view of some sharp criticism of American medicine.

The Board's primary conclusion was that the medical profession had failed to provide adequate health services for the vast majority of citizens and as a result the awakening consumer was left angered and frustrated. Health services were obtained "only when sickness or injury forced consumers to muster the money and risk the obstacles and humiliations." Once the decision was made to seek care, "many Americans have no choice of where or from whom to seek it." "Patients who overcome the barriers to care" the report continued, "may find themselves treated with indignity and insensitivity, and sometimes the line between insensitivity and poor quality care is blurred."

The report described the inadequacies of

Dissenting Opinion reprinted from "Heal Yourself"—Report of the Citizens Board of Inquiry into Health Services for Americans.

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* Available from Citizens Board of Inquiry into Health Services for Americans—c/o Harry Hoge, Executive Director, Arnold & Porter, 1229 19th St. N.W., Washington, D.C. 20036.

health insurance and hospital care as well as the providers acting from a narrow base of unrestrained professional interest. It decried decisions of the physician involving personal considerations that lead to overspecialization and maldistribution of providers.

Consumers are described as having "no real or effective role in the planning, organization or delivery of health care." And the report says further: "Like the doctors and the hospitals, the insurance industry has the consumer literally at its mercy. There is almost no opportunity for the health care consumer to influence the when, where and quality of services he receives or to determine how they should be paid for."

The recommendation of the Board to overcome the disarray of our health services is that it is "the responsibility of government, ultimately the federal government, to assure adequate health care for all Americans. Where care is inadequate, the federal government must become the residual guarantor, and, if necessary, the provider of health care."

The opinion submitted in rebuttal to the above summarized report follows.

Dissenting Opinion

This dissenting opinion is submitted because of some fundamental differences with the majority report. The undersigned, as a practicing physician and a concerned citizen, appreciates the opportunity to have served on this Board and the further opportunity to present this minority view.

There is an inherent bias in the rhetoric of the majority report, which serves no constructive purpose, and, in being accusatory rather than informative, does a disservice to a dedicated profession. Such rhetoric serves to undermine the cooperative effort between consumer, provider and government that is necessary if we are to correct the obvious and poignant inequities in the provision of health care.

It is regrettable that the provider is being discounted as a source of solution for the problems that this report documents. The right to health care must be guaranteed by our entire society, not the federal government alone. To suggest the latter would be a cruel hoax in raising expectations incapable of being fulfilled. The report, therefore, should have addressed our entire society, including the provider. To denigrate the

responsible role the provider must share in guaranteeing the appropriateness, relevance and success of solutions is a disservice to our democratic processes and our pluralistic heritage.

There is a further inherent bias in the selection of consumers for interview which was neither cross-sectional nor representative of all our people. Granting the limitations of time, staff and money that precluded an exhaustive and scientifically sound inquiry, the opinion that resulted from the sampling seems to imply that there is nothing worthwhile in the entire health effort in this country. There is evidence to the contrary, and to deny it undercuts the credibility of this report.

There is, finally, a deep concern about the process of writing a report such as this. It was necessarily written by staff, although the Board was given ample opportunity to react to it. The manner of collecting material, interpreting and presenting it, could only reflect the authors' views, as modified by the Board. No amount of suggestion for change, however, could reconcile fundamentally disparate views, hence this minority statement.

This dissenting opinion rejects the contention of the majority report that it has presented evidence of the gross national inadequacy of health services. What it has done is present the view of those bereft of health care because of their poverty and those who, because of their socio-culturally deprived life style, have strong deterrents to an optimal health state.

This dissenting opinion rejects the contention of the majority report that it has presented evidence for a single nationwide federal program as a solution for our health service problems. Such a simplistic conclusion is an interpretation that is neither supported by the interviews that make up the basis for this report, nor is based on hard data or dispassionate planning.

This dissenting opinion rejects the contention of the majority report that the consumers are powerless in relation to the provider. This cynical view completely ignores the existence of a professional ethic, the strength of consumer advocates and the rapidly emerging role of the consumer in all health policy matters.

This dissenting opinion rejects the inflammatory and emotional appeal by the majority report for crisis relief at any cost without concomitant long-range planning. Such an approach does not

do justice to the talents represented on this Board which are capable of sound inquiry, equitable judgment, and constructive proposals for change.

The following is a summary for the basis of this dissenting opinion:

(1) Adequacy of Health Services

There is no denying that many Americans have less than optimal health care. There is also no denying that the system may often be unresponsive to consumer needs. Nor is there any disagreement that we must, as a mature society, guarantee the right to health services for those in need, without the impediments of cost, inaccessibility or lack of responsiveness. The fundamental problem is to decide exactly how to achieve the greatest degree of equity in the provision of health services consistent with what our society establishes as its order of socio-economic priorities.

Health and Social Problems. While this entire report is ostensibly devoted to health, it is apparent to all that health is but a small aspect of one's socio-cultural well-being. To correct inequities in health care without simultaneously correcting inequities in housing, nutrition, education and environment is fruitless. One needs no documentation of the impact of poverty and its attendant evils on one's health state. To accuse the provider for these shortcomings, as the majority report implies, is inappropriate, as well as distracting from the basic problem. The problem is not lack of health services alone, but the entire culture of poverty. Culpability for these social problems cannot be laid at the feet of the provider. They are ageless and worldwide. We have an opportunity as a nation for the first time in history to overcome the deprivations of poverty and with it overcome the greatest impediment to adequate health services.

Health services also represent only a small fraction of one's general health state. The larger amount of one's health state revolves about life styles and habits, as well as his social environment. No amount of change in our health delivery systems will overcome the deaths attributable to auto accidents, smoking, or dietary excesses, to name only a few. Mortality statistics cannot be considered in a vacuum. A death from a late diagnosis of tuberculosis is no less than a death

due to an overdose of heroin. Studies of smokers clearly reveal a diminution in life expectancy of the heavy smoker by eight years, compared with the non-smoker. More than 600,000 persons in the United States die annually from heart disease. Consideration of parameters such as stress, smoking, lack of exercise and diet, all of which are matters of life styles, lends a somewhat different perspective on the true nature of the problems of health in this country. It may well be that the greatest area for improvement in the health state of the American public lies not in the improvement of health services, but rather with education and the assumption of individual responsibility for healthful life styles.

Health Services. There is no dispute that health services should be accessible, immediate, personal, unhurried, continuous, concerned and excellent, with no financial barriers. This is an ideal state and we should work towards it. It is a state of health care that is available to many in this country and it should be available to all. In a study done in our area [California], 1,500 households were involved in a survey of health needs. The sample was one-half of one percent of all households in the county. It was a statistically sound cross section of income, race, ethnic origin and geography. Our final results are not collated but it was surprising to find that 72 percent of respondents who were asked a series of questions about their care were satisfied with their health services. They were satisfied specifically with availability, accessibility and acceptability. While this was a small sample in one small corner of this great country, it was interesting enough for us to pause and wonder whether our perceptions of the inadequacy of health services in this country are based on dispassionately acquired data, or whether they are based on reports of that portion of our population that is devoid of optimal care and does need assistance. Shall we then base our decisions on national health policies on health services research or on political reactions to the selected anecdotes presented in the majority report?

(2) Disarray of our Health Delivery Systems

The problem also is stated to be that our health delivery systems are inefficient and uncoordinated and what is needed is a rational nationwide system. Furthermore, the majority re-

port continues, the marketplace is inappropriate for the provision of health care and should be dispensed with.

The concept of disarray, in contrast to orderliness, is a semantic trap. One could hardly argue against rationality, responsiveness, or orderliness, yet what do we hope to achieve in providing personal health care if not, in the ideal, an intensely personal service responsive to the patient's needs. Disarray, in one man's view, may well represent ideal personal encounter in another man's view. Nor can the so-called inefficiency of the personal encounter be faulted. On the contrary, anyone in need of health services needs, if nothing else, personal encounter. All our service industries do not lend themselves readily to the kind of productivity that has characterized our industrial economy. The healing arts, particularly, involve the human touch and the dedicated concern of a selfless and knowledgeable professional. To sacrifice this in the name of efficiency and a coordinated system would run against the tide that is rising in our national consciousness that the primary function of our institutions should be the fulfillment of human needs. This must be our focus and to ignore it would serve to increase the depersonalization and alienation that is so widespread today.

How then, are these needs best to be served, if not to provide for all what is possessed by those who are satisfied with their care. There are impediments and these should be removed. Manpower must be expanded as a vital national resource. Cost efficiencies must be enhanced by a variety of techniques, such as computer assistance, automated laboratories, peer review, ancillary health personnel and cost accounting. Any impediments to the growth of alternate delivery systems must be removed.

But diversity of choice cannot be so cavalierly dismissed by instituting a planned new delivery system for all. It is the marketplace that allows for the greatest sensitivity to individual needs. It is limitless in the options available, allows the one who *wants* to do the choosing as he sees fit, rather than having someone choose for him, is devoid of moralizing and draws no distinction among those who purchase. Against these benefits are the obvious critical shortcomings that needs are subservient to ability to pay. While it is true that the harsh inequities of the market

economy would be corrected by a new delivery system, other inequities will surely take their place. The forcing of our entire health venture into a single monolithic system, as the majority report recommends, would tend to freeze mistakes, stifle personal choice, diminish quality, and junk our pluralistic heritage. The public interest would be far better served to retain those portions of our system that are satisfactory, to restructure those aspects of our system that are unsatisfactory, and to create new ones where they are lacking. Pluralism in the provision of health services should be maintained. A basic minimum can be provided for all in this context.

(3) Centralized vs. Decentralized Loci of Authority

In some circles there is a conventional wisdom that the majority report promulgates, that if there is a problem that affects us all, the solution must be provided by the federal government. This is often expressed by clichés suggesting that the federal government must assume responsibility if individuals or institutions don't do what needs to be done or if they solve problems in a piecemeal rather than a national fashion.

Inherent in these arguments is the idea that there is an omniscience and omnipotence in Washington which would provide by a stroke of the pen on just the right document the instant and all-pervading solution. Nothing could be further from the truth, as is painfully evident to all citizens who have recognized the vast gulf between federal promise and performance. Our only protection against this gulf is to keep the locus of decision as peripheral as possible and maintain a regional and local approach to solutions that allow for the greatest degree of responsiveness possible. This is the basis on which the Partnership for Health and Regional Medical Programs are functioning and both are attracting wide attention as successful models for federal, state and local relationships. Within broad guidelines from the center, the locus of decision and authority functions best when kept as close as possible to the source of need.

Implied threats of assumption of authority by Washington are empty because an informed citizenry is well aware of the technical impossibility of the provision of services by the federal establishment or the instant creation of an entire new infrastructure for the provision of health services.

The federal role in this context is best described by the report of the Task Force on Medicaid and Related Programs: "The task force sees management of the system as given direction by federal leadership, specifically in the Department of Health, Education and Welfare. As is envisioned and recommended here, the management function for the health care system is to be innovative but not prescriptive; bold, but not authoritarian. It is the intention that the federal leadership, as far as possible, shall guide, not direct; motivate, not demand; assist, not provide; and evaluate, not ordain."

(4) Consumer Control in Health Policy

There is no question that the entire health effort must be focused on consumer needs. Any institution devoted to health services, old or new, must have a structure responsive to the consumer.

In the absence of this responsiveness, no amount of consumer control will bring about a desired end. The critical aspect of the consumer's position must be to have a formal opportunity for molding the institution to his needs. In the relationship between patient and physician, this is done in endless encounters based on mutual trust and the satisfying of patient needs. If the institution is other than a one-to-one patient-physician encounter, the establishment of policy must be based on a dialogue between provider and consumer by bringing both representatives together to see how needs are not being fulfilled. Policy decisions must be joint decisions. What is important is the creation of an established methodology for assuring both the dialogue and response to the decision. In this context, the seat of power is of secondary importance, since both provider and consumer are indispensable to the service.

The early history of consumer-dominated organizations for health care delivery has been extremely variable and not all favorable. Some Comprehensive Health Planning Agencies, Neighborhood Health Centers, and Regional Medical Programs have demonstrated a brilliant coordinated effort between provider and consumer. However, often the consumers' numerical presence is a ruse for the retention of an inadequate but established lack of responsiveness. Where policy decisions must be based on technical competence, the inept organizational structure that allows such decisions to be made by the consum-

ers who don't have such technical competence undercuts the credibility of the organization. Consumer representation is also often only a token by the choice of acceptable but impotent representatives.

This minority report agrees that consumer representation must not be a sham nor should providers be responsible for contribution to policy decision if there is any conflict of interest. The essential ingredients for an effective, responsive institution are clearly articulated needs, shared control and responsiveness of provider to policy-making bodies that function as community trustees. The majority report seems to be a clarion call only for the assumption of power and not a search for equity.

(5) Planning—Problem Solving vs. Goal Achievement

The majority report calls for an urgent response to a crisis in health care. Perhaps the greatest difficulty encountered by planning groups, however, is the juxtaposition of planning for the achievement of long-range goals and, at the same time, solving urgent problems. Our national health effort has been characterized by an emphasis on the latter and the almost complete ignoring of the former. Both are simultaneously necessary. Unless we set our goals for some fixed time in the future and plan a series of intermediate objectives along a reasonable time scale, we can never move towards the realization of aspirations, except accidentally in the course of heading off one crisis or another. The current stampede towards a universal Federal Health Insurance Program exemplifies the dilemma. No amount of delivery system restructuring or payment mechanisms restructuring can provide adequate care without expanding our manpower resources simultaneously. As we embark on a new national venture in the absence of long-range plans, we will replace present crises with new ones.

It is in this context that this minority report expresses its greatest concern. There is no denying that the poignant inequities described in the majority report do exist. It is feared, however, that the emotionalism engendered by the presentation will serve as a stimulus for the further headlong rush, without planning and rational study, into a system that may create more prob-

lems than it will solve and leave us further from the ideal than previously.

By all means, let us jointly work towards solving our pressing health problems as equitably and expeditiously as possible. But let us also, at the same time, define our long-range ideals and set about systematically for their achievement.

Conclusions: This minority report is presented not to dispute the documentation of need and inequities described by the majority report but rather to have the reader consider the conclusions reached based on the following caveats:

That personal health is part of one's milieu. It cannot be improved alone but in the context of other basic social conditions.

The health services contribute to but a small part of one's health state. Mounting a national effort to enhance health services without affecting life styles and the hazards of our culture and environment will do little to ameliorate our national health state.

That in the absence of a dispassionately acquired body of knowledge about health services, we may grossly misdirect a national health effort based on political reaction to poignant anecdotal wisdom.

That in our zeal and our passion for order, we may uncritically reject the primacy of the unhurried human touch in the rendering of personal health services and sacrifice it to the efficiency of a single monolithic health system.

That the obvious inequities in our health care are correctable without relegating the provision of care to the federal government or a new health care infrastructure. Manpower shortages are amendable by the expansion of this national resource. Distributive shortages are amendable by periods of obligatory service or financial incentive. Individual poverty or medical indigency may be amendable by the provision of funds for those in need. Delivery systems that are inadequate for the culture of poverty may be restructured to meet those needs.

That dialogue between provider and consumer acting as community trustees rather than power struggles of vested interests will best serve consumer needs.

That the locus of authority for health decisions should be as peripheral as possible. Central function should be to provide coordination, guidance, and resource assistance.

That solving health crises alone will only replace one set with another. There is urgent need for concomitantly planning our future in health care and achieving it only by incremental achievement of intermediate planned objectives.

That ultimately our problems revolve around our choice of national priorities. Human needs and the quality of our lives must be our focus. Our affluent society cannot tolerate the gross social inequities that this report documents. In the necessities of life, a basic minimum for all is economically feasible, just and timely.

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TREATING THE PAIN OF AORTIC ANEURYSM

We think it's very important in the patient with an acute dissecting aortic aneurysm to relieve pain. For instance, if the patient comes in with severe back pain, we lower the blood pressure to an appropriate level, and the back pain is relieved; then we feel comfortable in assuming that the dissection has been arrested and that everything is under control. On the other hand, if we lower the blood pressure and the pain is not relieved, we think this means the dissection has not been arrested and further measures must be taken. Under such circumstances, we would not hesitate and have not hesitated to lower the blood pressure to 70 or 80 mm of mercury systolic, provided the patient could continue to maintain a urinary output of a minimum of 25 mm per hour. In other words, one looks at the cerebration and the pain on one end and the urinary output at the other and this is the way these patients are monitored clinically.

—MYRON W. WHEAT, JR., M.D., Gainesville, Fla.
Extracted from *Audio-Digest Internal Medicine*, Vol. 17, No. 8, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 619 S. Westlake Ave., Los Angeles, Ca. 90057

Physicians' Benevolence Fund

CLYDE L. BOICE, M.D., *Palo Alto*

AFTER HIS INTERNSHIP AND army duty, the young physician finished his residency and started to establish his own practice. The practice began to prosper after several years and he negotiated to buy a home. Then disaster struck. A tumor was discovered and its removal resulted in medical complications so severe that the young physician no longer was able to work.

Under close medical supervision for some ten years and with further extensive surgical operation necessary, he watched all his resources disappear. He lived in a borrowed house and his only income came from small monthly disability insurance payments and the little that relatives could spare. Superimposed on all these difficulties was a separate illness, encephalitis.

Where could this doctor turn for help? Like many other needy California physicians before him, he discovered that his colleagues maintain an organization to help in times of severe need. The Physicians' Benevolence Fund, Incorporated, was contacted and he received assistance for several years. Today, largely because of this help, the doctor is back in practice and again an active member of his community.

A number of state medical associations have doctor-welfare organizations which offer financial help ranging from small payments to a widow to an allotment for an indigent physician's entire family. But California's Physicians' Benevolence Fund is an outstanding example of these programs and unique in several ways.

What are some of the benefits offered by the Benevolence Fund? It provides aid for needy doctors incapacitated by crippling diseases or

injuries. It also helps tide their families over difficult periods when they are deprived of a breadwinner. In case of sudden death the Fund helps sustain the widow and minor children until she can find employment. In many instances it has helped a doctor's children to complete their education in order to become self-supporting and able to assist with family problems. The Fund has aided elderly physicians and their wives when assets dwindled, making it possible for them to remain in their own homes or apartments.

One noteworthy feature of California's program is the support given to the Physicians' Home and Elizabeth Manor Sanitarium in Los Angeles. These institutions, operated by the Los Angeles County Physicians Aid Association, receive financial assistance from the Fund—a situation unique to California. The two facilities are available, as space permits, to members of the California Medical Association, their wives, widows, and parents. Those who live in the home and sanitarium pay what they are able, and naturally everyone receives the same care regardless of financial circumstances.

Incorporated in 1955, the Fund has assisted physicians and their families in a wide range of difficulties during the last 16 years. Many of these problems stem from the effects of unexpected and catastrophic illness.

One recipient of aid had practiced in a large California city for nearly 20 years. But, after being stricken with multiple sclerosis, he was confined to a wheelchair. He had completely lost the use of both legs and one arm. His insurance benefits and savings were exhausted. His wife was unable to work. Once again, the Fund pro-

Chairman, Operating Committee of Physicians' Benevolence Fund, Inc.

Reprint requests to: Physicians' Benevolence Fund, Inc., 693 Sutter Street, San Francisco, Ca. 94102 (Mr. L. O. Hetland).

vided financial assistance. In addition, the disabled physician, whose mind remained extremely alert, was put in touch with a non-profit organization that could make good use of his medical knowledge.

In some cases, the original plea for assistance comes from the physician himself. On other occasions, the Fund has helped support destitute physicians through the intercession of their families or even through comparative strangers. This was the case with the assistance rendered to an 84-year-old general practitioner. He had never earned a large income and a long and costly bout of illness left him penniless. After an operation he was scheduled to be released from hospital but his wife who subsisted on a small Social Security check, was unable to care for him or provide for a nursing home.

This was the elderly doctor's situation when it was brought to the attention of the Fund by a local physician. Working closely with the doctor's wife, the Fund assisted with money for nursing home care through the remaining three years of the doctor's life. In addition financial help was given to his wife, making it possible for her to keep the small house she occupied.

The Fund's assistance doesn't always stop with a physician's death. His family is often helped long after he is gone. The elderly wife of a Northern California physician was left in need after her husband died. Receiving monthly Old Age Assistance checks from the state, she was accepted in a home for the elderly. However, after her room and board were paid, she was left with very little money for personal expenses. The Physicians' Benevolence Fund assisted her with paying necessary expenses as they occurred. When she needed a new mattress and several other personal effects, the Fund came to her aid. She was also helped to make a visit to her daughter. She received small amounts from time to time to provide for occasional needs. While the actual amount of money expended was not large, it was greatly appreciated and served to make her life more bearable.

As these cases illustrate, doctors are not immune to hard luck or dire poverty. For these reasons the Physicians' Benevolence Fund was incorporated to "engage in the primary activity of granting financial aid and assistance to needy members of the California Medical Association and their dependents."

The need for such aid is increasing rather than diminishing, and more and more county medical society aid programs are now augmenting the state association project. At present, income for Physicians' Benevolence is derived from one dollar a year from each California Medical Association member's dues, from voluntary contributions from the Woman's Auxiliary, and from interest earned on investments. Financial help by the Auxiliary has assisted greatly, with \$4,356 contributed during the year 1970-71.

Support for the Benevolence Fund by the Auxiliary has not been limited to financial contributions. The members of the Auxiliary have contributed many hours of work on behalf of the Fund and its beneficiaries. When a request is received for assistance, the state liaison representative from the Auxiliary contacts a member in the applicant's local area. She in turn visits the applicant and estimates the extent of need. Increasingly, the Auxiliary also is making periodic visits to Fund beneficiaries—those in old age homes, for example—to be certain they are well and to find out if there is anything more the Fund might do. These services provide invaluable help to the Benevolence Fund—and help obtainable in no other way.

Requests for help come in many forms, though a formal application must eventually be made to the Benevolence Fund. These applications are considered by the seven-member Operating Committee by phone, mail, and at its regular meetings. Since the intent of Benevolence Fund assistance is short-range help in time of crisis, the Committee places emphasis, when possible, on making recipients once again self-sufficient. When the Benevolence Fund receives an application, every effort is made to spare the applicant embarrassment. This emphasis on keeping all dealings confidential is a major factor in the success of the Fund.

Physicians and their wives may assist the Benevolence Fund by bringing needy cases to the attention of the Operating Committee for Physicians' Benevolence, 693 Sutter Street, San Francisco, California 94102. Contributions may be made directly to the Fund. Checks should be made out to Physicians' Benevolence Fund, Inc. Such gifts might be considered in lieu of flowers at funerals.

CBS/CMA Relationships

In response to the House of Delegates action, March, 1971, on the report of the ad hoc Committee to Study CBS/CMA Relationships, the conclusions and recommendations of the ad hoc Committee and the actions taken by the House of Delegates on those recommendations, are published below.

Conclusions of the ad hoc Committee to Study California Blue Shield/CMA Relationships Final Report to the House of Delegates

Based on close and careful study of the relevant data collected, and taking into consideration the various recommendations submitted by physicians throughout the state, the Committee has arrived at the following conclusions:

1) Though California Blue Shield has improved its operation and management in the recent past, numerous problems still do exist. These were compounded by the advent of such government health programs as Medi-Cal. The difficulties generated by Medi-Cal, for example, have also caused CBS to give inadequate attention to their standard programs. There is an apparent need for widespread changes in management organization and procedures.

2) There is significant physician dissatisfaction with many aspects of California Blue Shield's operation. This dissatisfaction is especially apparent in relation to the Medi-Cal program. Inadequate communication between CBS and individual physicians is one major cause of this problem.

3) While it may have been responsive to its Board of Trustees, California Blue Shield has not been adequately responsive to the CMA Council, the needs of individual physicians, and the problems of local medical societies. There is evidence showing unnecessary annoyance of physicians with billing, rebilling, reports, and superfluous correspondence. It appears that this lack of responsiveness may result, at least in part, from the present indirect method of nominating members to the Board of Trustees.

4) Considering the widespread physician discontent with California Blue Shield, management appears to have an inadequate understanding of the acuteness of the contributing problems. A large number of physicians consider CBS unwilling or unable to provide adequate solutions to the problems confronting the organization.

5) California Blue Shield has been deficient in its manner and procedures of claims processing. There has been too much centralization of this activity and a failure to fully utilize services of

local medical consultants and local medical society review committees. RVS code numbers as indicated by physicians have frequently been changed in what seems to be an extremely arbitrary manner. It also appears that decisions are sometimes made by the Medical Policy Committee without considering the best interests of the physicians affected.

6) The CMA Council has not assumed the necessary degree of advocacy for individual physicians in their complaints with CBS, nor always realized its responsibility to see that CBS is working efficiently. Furthermore, CMA should have more effective control over the policies of CBS. When government speaks to CBS, it should be speaking to organized medicine (such as the ad hoc Committee on Medi-Cal Prepayment), rather than to administrators.

7) Although California Blue Shield's operations as a fiscal intermediary for government programs often have been a source of irritation, physicians would generally have experienced more difficulty had not CBS acted as a buffer between the physician and government.

8) Responsibility for the adoption of a "profile system" did not originate with CBS, but rather constituted a computerized response to the House of Delegates' request for a system by which the carrier should be able to pay "usual, customary or reasonable" fees. In regard to CBS standard business, discontinuation or alteration of the profile system could be authorized by the House of Delegates of CMA. This is not true in programs under governmental sponsorship, however. In these instances, the profile system can be changed only by appropriate governmental agencies.

9) The Medical Policy Committee of the CBS Board of Trustees has not adequately represented California's physicians, nor has it been adequately sensitive or responsive to their wishes. There is a definite need for some mechanism to insure that decisions made by the Medical Policy Committee do not conflict with the policy and aims of CMA, or those of individual physicians.

Recommendations of the ad hoc Committee to Study California Blue Shield/CMA Relationships
and

Actions of the House of Delegates, March 1971

1) The Committee is unanimous in its opinion that a close relationship between CMA and California Blue Shield should be maintained and improved. To this end, one essential step is the establishment by California Blue Shield of regular and adequate systems of communication between CBS and the California Medical Association on every level: 1) CBS Board of Trustees and CMA Council (President of CBS or Chairman of CBS Board of Trustees to report at each "Family" Session of the CMA Council); 2) the two Executive Committees, and 3) the CBS and CMA staffs.

ACTION: Adopted as amended.

Referred to: CBS Board; Council; Executive Committee; new Liaison Committee; Executive Director.

2) The Board of Trustees of California Blue Shield has the responsibility and obligation to make a comprehensive reappraisal of CBS management's efficiency. Necessary changes should be implemented.

ACTION: Adopted.

Referred to: CBS Board of Trustees.

3) The Committee is also unanimous in its opinion, after hearing pros and cons of testimony, that CBS should continue to serve as the fiscal intermediary under government programs.

If the Department of Health Care Services is to continue its involvement with the functioning of the Medi-Cal program, an attempt should be made to re-negotiate the CBS Medi-Cal contract with that department in order to eliminate the gross injustices forced on CBS in its role as a fiscal intermediary. Without question, these problems have been a cause of major difficulties and dissension between California physicians and CBS.

ACTION: Adopted.

Referred to: CBS Board of Trustees.

4) Since hospitalization accounts for a substantial proportion of the health care dollar, and since Blue Cross is the pre-eminent mechanism in that field, it is recommended that study be given to developing a companion relationship between Blue Cross and CBS in all lines of their business. The creation of one unified and representative Board of Trustees also should be studied and reported on as expeditiously as possible.

ACTION: Adopted.

Referred to: CBS Board of Trustees.

5) Though not specifically charged with making recommendations relative to the general fiscal operations of California Blue Shield, the Committee feels that further information in this area is needed by the California Medical Association. It is recommended that a detailed review of relevant CBS administrative fiscal procedures and organizational solvency be undertaken immediately as a housekeeping task and that this be repeated annually.

ACTION: Adopted.

Referred to: CBS Board of Trustees; new Liaison Committee.

6) The Medical Executives Conference, in conjunction with CMA staff, should devote a portion of its regular sessions to meeting with representatives of California Blue Shield. CBS should be encouraged to invite representatives of the Medical Executives Conference to attend meetings of its Board of Trustees and Medical Policy Committee.

ACTION: Adopted.

Referred to: CBS Board of Trustees; Executive Director; Medical Executives Conference.

7) CBS's local Medical Advisor System should be altered and strengthened. Claims that require the use of local medical advisors should be referred to the office of the local medical executive secretary and to individual members serving on the local review committee. These individuals must be in a position to pass judgment and call their opinions to the attention of the review committee as a whole. A system must be established by which individual physicians can obtain necessary information about claims in process in an expeditious manner. The need for adequate funding under government programs for the establishment of a "random access" system must be emphasized. RVS code numbers must not be arbitrarily changed and, on the rare occasions when such changes are justifiable, they should always be authorized by a physician reviewer and the reasons for the change should be made clear to the physician who submitted the original claim.

ACTION: Adopted.

Referred to: CBS Board; Liaison Committee.

8) CBS must accelerate its efforts to improve both oral and written communications to providers and consumers of services. Clear, meaningful explanations are necessary when claims must be returned to physicians for correction.

ACTION: Adopted.

Referred to: CBS Board of Trustees.

9) Governmental agencies must not be allowed to use CBS letterhead to announce decisions arrived at by government or to censor communications between CBS and physicians.

ACTION: Adopted.

Referred to: CBS Board of Trustees.

10) Two policy changes are needed to improve California Blue Shield's relationship with the profession at the local level:

a. The reduction in the CBS Field Services Division has produced problems in the smaller communities. Where there is no Field Representative Office, the medical executive of the component society or CMA field staff should be utilized to the fullest extent possible.

b. In counties where foundations for medical care exist, CBS should make use of their facilities for the local review of claims whenever feasible. CMA should work closer with Foundations. CMA should attempt to influence the component societies to instruct their foundations to work closely with CBS. Innovation must be encouraged while, at the same time, avoiding further fragmentation of the profession.

ACTION: Adopted as amended.

Referred to: CBS Board of Trustees; Commission on Medical Services.

11) In regard to those CBS policies and procedures which create problems for physicians, CMA must take a more positive stance in support of the physician. CMA is morally and ethically obligated to seek revision of such policies and procedures.

ACTION: Adopted.

Referred to: Council; New Liaison Committee.

12) Medical Policy Committee appointments: a) the existing method of the appointment of the members of the Medical Policy Committee be retained, b) the CMA Council designate the chairman and a member of the Committee on Relative Value Studies to serve on the CBS Medical Policy Committee, and c) decisions made by the Medical Policy Committee be submitted to

the CBS Board of Trustees and simultaneously be submitted to the CMA Council.

ACTION: Substitute recommendation adopted.

Referred to: CBS Board of Trustees; Committee on Nominations.

13) The House of Delegates should appoint an ongoing committee with the function of periodically reviewing and assessing relationships between the members of CMA and CBS, as well as with other fiscal intermediaries for government programs. This committee should be required to report to the CMA Council no less frequently than semi-annually.

ACTION: Adopted.

Referred to: Speaker to appoint.

14) Since the CBS "profile system" is not functioning as originally intended, it should be given thorough study resulting in either specific recommendations for improvement or consideration of possible abandonment. In addition, the future prospect of utilizing "patient profiles" should be considered.

ACTION: Adopted.

Referred to: Council Ad Hoc Committee on UCR and Profile System (see Resolution 97-71). Speaker to appoint.

15) In order to strengthen the relationship between CMA and CBS, it is the recommendation of the Committee that the following changes be made in the method of selecting the CBS Board of Trustees:

a. No more than three members of the CMA Council may be members of the CBS Board of Trustees and that these members shall be prohibited from serving either as chairman or vice-chairman of the CBS Board of Trustees.

b. All other physician members of the Board of Trustees shall be elected by the House of Delegates. Nominees for these positions should be processed by the Committee on Nominations of the CMA, as is customary for nominations to all committees and commissions of the Association. The Committee feels that the Committee on Nominations should actively solicit suggestions from all county societies for nominees for these positions but may also receive nominees from the Council of the CMA. The Board of Trustees of CBS should submit names of non-physician members to the Committee on Nominations to fill any appropriate vacancies. The Committee fully realizes that the implementation of these suggestions will require a change in the CBS Bylaws.

ACTION: Above recommendation adopted as amended.

Referred to: CBS Board of Trustees; Committee on Nominations.

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The editors wish to acknowledge with appreciation the valued services, beyond those of members of the Editorial Board, given by the following persons to the Journal during the past year.

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Elizabeth Barrett-Connor
Howard S. Barrows
Talcott Bates
Charles E. Becker
Folkert O. Belzer
John Biles
Walter D. Birnbaum
F. William Blaisdell
Leland B. Blanchard
Edward R. Bloomquist
Edwin B. Boldrey
Henry B. Bourne
Lloyd Brandborg
Abraham I. Braude
George Brecher
Barry Brenner
Ellen Brown
Howard A. Brown
Lewis T. Bullock

John V. Carbone
Erik S. Carlsson
Charles T. Carman
Robert A. Chase
Martin J. Cline
Richard J. Cohen

Stephen N. Cohen
John Conte, Jr.
Alvin J. Cox
Robert K. Creasy
Robert Crede
Lawrence G. Crowley
Benjamin L. Crue, Jr.
Francis Curry

Seymour Dayton
Herbert H. Dedo
David J. Drutz
J. Engelbert Dunphy

Laurence E. Earley
L. Henry Edmunds, Jr.
Charles J. Epstein
Wallace V. Epstein

Ames Fischer

Warren Gold
Alan Goldfien
Leon Goldman
Mervyn J. Goldman
Robert Goldsmith
Gilbert S. Gordan
Frank Goteh
Jere E. Goyan
Francis Greenspan
Margaret Griffith
Maurice Grossman
Moses Grossman
Melvin M. Grumbach

Paul F. Gulyassy
Lucien Guze

Albert Hall
Beatrix A. Hamburg
William K. Hamilton
Donald C. Harrington
Howard Hassard
Richard J. Havel
Robert S. Hepler
George H. Herzog, Jr.
Donald Heyneman
Frank Hinman, Jr.
Paul D. Hoeprich
Michael Hogan
Milton Hollenberg

H. Dean Hoskins
Thomas Hunt

Leo Indianer
Verne T. Inman
Edwin M. Jacobs
Ernest Jawetz
Michael Jones
Rayford Scott Jones

John P. Kane
Hilliard J. Katz
Joseph W. Kaufman
Ronald L. Kaye
Emmett L. Kehoe
James P. Kemp
Keith Killam

Charles R. Kleeman
Murray Klutch
Felix O. Kolb
Samuel L. Kountz
Bernard M. Kramer

Joseph W. Landau
Glenn Langer
P. Herbert Leiderman
Dorinda Loeffel
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Alan J. Margolis
Judd Marmor
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Telfer B. Reynolds
Tom W. Robinson
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C. Peter Rosenbaum
Edwin F. Rosinski
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Edwin R. Sehattstaedt
Barbara Sehrier
Robert W. Sehrier
Stanley Sehrier
Arthur Selzer
Edward Shapiro
Marvin J. Shapiro
Edward B. Shaw
Martin Shearn
Morley M. Singer
Maurice Sokolow

David Solomon
Francis A. Sooy
Thomas A. Stamey
Howard Steinbaeh
W. Eugene Stern
Robert Stoller
Ronald J. Stoney

Norman Talal
Boyd Thompson
Malcolm C. Todd
Robert E. Tranquada
Charles John Tupper

William N. Valentine
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Vieki J. Wagner
Ralph Wallerstein
Leonard F. Walts
Lawrence W. Way
Morton R. Weinstein
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Henry Wheeler
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Hibbard E. Williams
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Woman's Auxiliary
David A. Wood
Henry H. Work
Edwin J. Wylie

Joe Yamamoto

David Zakin

In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

ARNOFF, WILLIAM HARRY, Palo Alto. Died October 9, 1971 in Mountain View of heart disease, aged 52. Graduate of Chicago Medical School, 1946. Licensed in California in 1969. Doctor Arnoff was a member of the Santa Clara County Medical Society.

AYERS, ROBERT L., Marysville. Died March 17, 1971 in Marysville of malignant disease, aged 61. Graduate of University of California Medical School, Berkeley—San Francisco, 1937. Licensed in California in 1937. Doctor Ayers was a member of the Yuba-Sutter-Colusa County Medical Society.

BENSON, CLARENCE, Sacramento. Died October 22, 1971 in Cambridge, Massachusetts, aged 42. Graduate of University of Illinois College of Medicine, Chicago, 1955. Licensed in California in 1961. Doctor Benson was a member of the Sacramento County Medical Society.

BRIFMAN, THEODORE, Sacramento. Died October 11, 1971 in Sacramento, aged 50. Graduate of Harvard Medical School, Boston, 1949. Licensed in California in 1950. Doctor Brifman was a member of the Sacramento County Medical Society.

CARLISLE, PAUL W., Redlands. Died October 12, 1971 in Loma Linda, aged 53. Graduate of College of Medical Evangelists, Loma Linda—Los Angeles, 1944. Licensed in California in 1944. Doctor Carlisle was a member of the San Bernardino County Medical Society.

CARLSON, EDWARD A., Stockton. Died October 13, 1971 in San Andreas, aged 50. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1952. Licensed in California in 1956. M.D. degree from California College of Medicine, 1962. Doctor Carlson was a member of the San Joaquin County Medical Association.

COLEMAN, HAROLD S., Beverly Hills. Died October 12, 1971 in Los Angeles of cardiac arrest, aged 53. Graduate of University of Illinois College of Medicine, Chicago, 1943. Licensed in California in 1945. Doctor Coleman was an associate member of the Los Angeles County Medical Association.

DALTON, ERIC G., Sausalito. Died September 15, 1971, aged 38. Graduate of University of Western Ontario, Faculty of Medicine, London, Ont., 1958. Licensed in California in 1964. Doctor Dalton was a member of the San Francisco Medical Society.

FIRESTONE, GEORGE M., Santa Rosa. Died October 18, 1971 in Sacramento of dissecting aneurism, aged 52. Graduate of The University of Minnesota Medical School, Minneapolis, 1943. Licensed in California in 1946. Doctor Firestone was a member of the Sonoma County Medical Association.

GONZALES, FLORENTINO A., Salinas. Died October 16, 1971 in Singapore of coronary thrombosis, aged 52. Graduate of University of the Philippines College of Medicine, Manila, 1946. Licensed in California in 1951. Doctor Gonzales was a member of the Monterey County Medical Society.

HOWSON, CARL ROBERT, Pasadena. Died September 29, 1971 in Pasadena of bronchopneumonia, aged 86. Graduate of College of Physicians & Surgeons, Medical Dept., University of Southern California, 1913. Licensed in California in 1913. Doctor Howson was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

KAFFESIEDER, LEWIS I., Los Angeles. Died October 26, 1971 in Los Angeles of pneumonia, aged 74. Graduate of Rush Medical College, Chicago, 1922. Licensed in California in 1923. Doctor Kaffesieder was a member of the Los Angeles County Medical Association.

LANE, ARTHUR R., Santa Barbara. Died October 16, 1971 in Santa Barbara, aged 51. Graduate of The Chicago Medical School, 1946. Licensed in California in 1953. Doctor Lane was a member of the Santa Barbara County Medical Society.

LEARY, JAMES JEREMIAH, JR., San Francisco. Died October 25, 1971 in Lanai, Kauai, Hawaii of cerebral vascular accident, aged 59. Graduate of University of California Medical School, Berkeley—San Francisco, 1937. Licensed in California in 1937. Doctor Leary was a member of the San Francisco Medical Society.

LINDSAY, CHARLES V. SR., Ocotillo. Died October 14, 1971 in Oceanside, aged 72. Graduate of College of Medical Evangelists, Loma Linda—Los Angeles, 1924. Licensed in California in 1924. Doctor Lindsay was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

**

MACDONALD, WILLIAM HUGH, Bakersfield. Died October 8, 1971 in Bakersfield, aged 68. Graduate of Rush Medical College, Chicago, 1937. Licensed in California in 1937. Doctor MacDonald was a member of the Kern County Medical Society.

**

MARSHALL, IRVING ARTHUR, Sherman Oaks. Died September 30, 1971 in Burbank of leukemia, aged 60. Graduate of Emory University School of Medicine, Atlanta, 1937. Licensed in California in 1947. Doctor Marshall was a member of the Los Angeles County Medical Association.

**

MARTINE, PAUL HENRY, Fullerton. Died March 8, 1971 in Fullerton of coronary thrombosis, aged 43. Graduate of Laval University Faculty of Medicine, Quebec, 1955. Licensed in California in 1964. Doctor Martine was a member of the Orange County Medical Association.

**

MULLENIX, RALPH B., San Diego. Died October 8, 1971 in La Jolla, aged 67. Graduate of Northwestern University Medical School, Chicago, 1933. Licensed in California in 1937. Doctor Mullenix was a member of the San Diego County Medical Society.

**

NUNN, WILLIAM EVANS, Los Gatos. Died October 8, 1971 in Los Gatos, aged 45. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1948. Licensed in California in 1952. Doctor Nunn was a member of the Santa Clara County Medical Society.

ROHLFES, BERNHARD JOSEPH, San Francisco. Died October 16, 1971 in San Francisco, aged 79. Graduate of Medizinische Fakultät der Christian-Albrechts-Universität, Kiel, Schleswig-Holstein, Germany, 1921. Licensed in California in 1926. Doctor Rohlfes was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

**

SCHWARTZ, HERBERT PERRY, Santa Monica. Died October 2, 1971 in Northridge of myocardial infarction, aged 53. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1943. Licensed in California in 1943. M.D. degree from California College of Medicine, 1962. Doctor Schwartz was an associate member of the Los Angeles County Medical Association.

**

SHAW, LYSLE ORTING, Paramount. Died September 21, 1971 in Bellflower, aged 76. Graduate of Detroit College of Medicine and Surgery, Detroit, 1916. Licensed in California in 1932. Doctor Shaw was a member of the Los Angeles County Medical Association.

**

STEPHENSON, HENRY A., San Francisco. Died October 19, 1971 in San Francisco of heart disease, aged 84. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1910. Licensed in California in 1914. Doctor Stephenson was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

**

STEPHL, PAUL DAVID, Van Nuys. Died September 28, 1971 in Encino of subarachnoid hemorrhage, aged 36. Graduate of University of Wisconsin Medical School, Madison, 1959. Licensed in California in 1961. Doctor Stephl was a member of the Los Angeles County Medical Association.

**

TODD, MAX A., Arcata. Died September 28, 1971 in Trinity County, aged 59. Graduate of Stanford University School of Medicine, Palo Alto—San Francisco, 1937. Licensed in California in 1937. Doctor Todd was a member of the Humboldt-Del Norte County Medical Society.

INDEX

Volume 115 July-December 1971

AUTHOR INDEX

	PAGE		PAGE
A		Dramov, Borina, San Francisco.....	(Sep) 64
Anderson, Carl E., Santa Rosa.....	(Sep) 74	Drutz, David J., San Francisco.....	(Oct) 34
Anderson, Elmer A., Los Angeles.....	(Nov) 65	Dubou, Richard, San Francisco.....	(Sep) 64
Anderson, William L., San Francisco.....	(Nov) 1	E	
Anhalt, James E., Jr., Bakersfield.....	(Nov) 56	Earley, Laurence E., San Francisco.....	(Nov) 23
Aronow, Wilbert S., Long Beach.....	(Sep) 16	Epstein, Charles J., San Francisco.....	(Jul) 76
B		Epstein, Ervin, Oakland.....	(Aug) 6, (Nov) 7
Barrett, Paul, Los Angeles.....	(Jul) 96	Escamilla, Roberto F., San Francisco.....	(Dec) 72
Barrett-Connor, Elizabeth, La Jolla.....	(Aug) 24	F	
Baxter, William, Los Altos.....	(Sep) 72	Flinn, Don E., Los Angeles.....	(Jul) 88
Beauchamp, Charles J., Travis Air Force Base.....	(Aug) 1	Fogarty, Thomas J., Stanford.....	(Nov) 61
Becker, Charles E., San Francisco..	(Oct) 5, (Nov) 42	Forsham, Peter H., San Francisco.....	(Dec) 72
Bennett, John V., Atlanta.....	(Oct) 56	Freedman, Lawrence D., La Mirada.....	(Aug) 24
Bergeron, Dale A., San Francisco.....	(Oct) 55	Freeman, Larry, Irvine.....	(Jul) 96
Besson, Gerald, Sunnyvale.....	(Dec) 79	G	
Bick, Rodger L., Bakersfield.....	(Nov) 56	George, Ralph P., Stanford.....	(Sep) 61
Biglieri, Edward G., San Francisco.....	(Dec) 40	Gilman, Nelson J., Los Angeles.....	(Oct) 67
Blaskovics, Milan E., Los Angeles.....	(Jul) 42	Gitnick, Gary L., Los Angeles.....	(Dec) 1
Bloomquist, Edward R., Glendale.....	(Nov) 64	Godfrey, Thomas E., Loma Linda.....	(Oct) 1
Blumenthal, Sidney, Miami & New York City..	(Jul) 108	Goerke, L. S., Los Angeles.....	(Aug) 94
	(Sep) 91	Golden, Joshua S., Los Angeles.....	(Oct) 60
Boice, Clyde L., Palo Alto.....	(Dec) 86	Goldsmith, John R., Berkeley.....	(Sep) 55
Braff, Erwin H., San Francisco.....	(Oct) 75	Goldstein, Elliot, Davis.....	(Sep) 21
Bramham, James, Sacramento.....	(Jul) 100	Gonzalez, Richard I., San Mateo.....	(Aug) 25
Braun, Richard, Downey.....	(Nov) 11	Gottschalk, Louis A., Irvine.....	(Aug) 87
Brenner, Paul H., San Diego.....	(Jul) 20	Grausz, Henry, San Francisco.....	(Nov) 23
Brill, Norman Q., Los Angeles.....	(Sep) 11	Graves, Clifford L., La Jolla.....	(Sep) 73
Brosman, S. A., Torrance.....	(Aug) 32	Griswold, Herbert E., Portland, Ore.....	(Nov) 52
Bruyn, Henry B., Berkeley.....	(Nov) 51	Gurwith, Marc J., Stanford.....	(Dec) 63
Buff, B. Hugh, San Diego.....	(Jul) 102	H	
Bunow, M. A., Berkeley.....	(Oct) 69	Halstead, Bruce W., Colton.....	(Dec) 61
Butler, R. Melvin, Los Angeles.....	(Sep) 67	Hamburger, Robert N., San Diego.....	(Oct) 24
C		Harman, Charles E., Stanford.....	(Dec) 63
Churchill, Asa G., San Francisco.....	(Dec) 77	Harrison, Donald C., Stanford.....	(Nov) 61
Clark, Paul S., Anchorage.....	(Sep) 7	Hassard, Howard.....	(Jul) 82
Cohen, Richard J., San Francisco.....	(Oct) 10	Havel, Richard J., San Francisco.....	(Nov) 23
Cohn, Lawrence H., Stanford.....	(Nov) 61	Hewitt, William L., Los Angeles.....	(Dec) 1
Cohn, Roy, Stanford.....	(Sep) 1	Hinshaw, David B., Loma Linda.....	(Dec) 4
Connor, James D., San Diego.....	(Oct) 24	Hobel, Calvin J., Los Angeles.....	(Dec) 1
Craddock, C. G., Los Angeles.....	(Sep) 89	Hogan, Richard A., Sunnyvale.....	(Nov) 58
Crumpton, Evelyn, Los Angeles.....	(Sep) 11	Hopper, James, Jr., San Francisco.....	(Nov) 23
Cunningham, G. C., Berkeley.....	(Jul) 28	J	
Cushard, William G., Jr., Chicago.....	(Aug) 24	Jackson, E. W., Berkeley.....	(Jul) 28
D		Jafek, Bruce W., Los Angeles.....	(Sep) 67
Dempster, W. J., London.....	(Dec) 17	Jesse, Mary Jane, Miami & New York City.....	(Jul) 108
Didio, Joseph M., San Diego.....	(Jul) 20		(Sep) 91

K

Kassebaum, Donald G., Portland, Ore.	(Nov)	52
Kennedy, L. James, Jr., Stanford.....	(Jul)	84
Kent, John R., Long Beach.....	(Sep)	16
Kerr, John H., San Diego.....	(Oct)	24
Keys, Thomas F., Los Angeles.....	(Dec)	1
Kirkpatrick, John E., San Francisco.....	(Sep)	72
Kirshen, Edward J., San Diego.....	(Jul)	20
Knudsen, D. Frederick, Stanford.....	(Sept)	1
Kornfield, Harrison J., Sunnyvale.....	(Nov)	58
Krain, Lawrence Stirling, Los Angeles.....	(Jul)	38

L

LaDou, Joseph, Palo Alto.....	(Jul)	34
Lane, J. Michael, Atlanta.....	(Sep)	7
Leedom, John M., Los Angeles.....	(Nov)	16
Libby, Peter, La Jolla.....	(Jul)	96
Litwak, Robert S., New York City... (Oct)	80, (Nov)	79
Long, Marlene E., San Diego.....	(Jul)	102
Lovett, E. D., Clearlake Oaks	(Nov)	66

M

March, Harold W., San Francisco.....	(Nov)	1
Marlon, Anthony M., Stanford.....	(Nov)	61
Martin, Carroll M., San Francisco.....	(Oct)	55
Martin, Neil D., Travis Air Force Base.....	(Aug)	1
Mason, Cole, Los Angeles.....	(Oct)	60
Melmon, Kenneth L., San Francisco.....	(Jul)	58
Menkes, John H., Los Angeles.....	(Oct)	14
Merigan, Thomas C., Stanford.....	(Dec)	63
Merrill, John P., Boston.....	(Dec)	56
Mihara, Gladys, Stanford.....	(Jul)	1
Millar, Marcia, Stanford.....	(Jul)	1
Miller, James N., Torrance.....	(Aug)	47
Mitchinson, M. J., Stanford.....	(Jul)	84
Monie, Ian W., San Francisco.....	(Jul)	99
Mooney, Vert, Downey.....	(Nov)	11
Muldavin, Michael S., Berkeley.....	(Oct)	69

N

Nelson, James R., Torrance & San Diego.....	(Aug)	47
Nelson, Thomas L., Irvine.....	(Jul)	42
Nickel, Vernon L., Downey.....	(Nov)	11
Nowack, William J., Stanford.....	(Jul)	96
Nyhan, William L., San Diego.....	(Oct)	24, 57

O

Oakley, Celia, San Francisco.....	(Aug)	61
Oh, William, Los Angeles.....	(Dec)	1

P

Parker, Leonard M., Hayward.....	(Nov)	72
Pattison, E. Mansell, Irvine.....	(Aug)	87
Petit, Donald W., Alhambra.....	(Jul)	96
Petrakis, Nicholas L., San Francisco.....	(Dec)	77
Portnoy, Bernard, Los Angeles.....	(Nov)	16
Poth, James L., Stanford.....	(Sep)	61

Q

Quadracci, Leonard J., Seattle.....	(Sep)	57
-------------------------------------	-------	----

R

Raymond, Leland R., Loma Linda.....	(Dec)	4
Reisner, Ronald M., Torrance.....	(Aug)	47
Reiman, Arnold S., Philadelphia.....	(Dec)	58
Reznichuk, R. C., Torrance.....	(Aug)	32
Riggs, Mary, San Jose.....	(Oct)	75
Rimoin, David L., Torrance.....	(Aug)	75
Ritman, Susan, Los Angeles.....	(Dec)	1
Roizen, Michael, Boston.....	(Oct)	5
Roper, Brian, London.....	(Nov)	11
Rush, H. John, Sacramento.....	(Jul)	100

S

Sahud, Mervyn A., San Francisco.....	(Oct)	10
Salvatore, Margaret A., Los Angeles.....	(Nov)	16
Saylor, Louis F., Berkeley.....	(Jul)	106
	(Aug) 96, (Sep) 93, (Oct) 78, (Nov)	75
Schafer, Donald W., Irvine.....	(Aug)	87
Schiller, Francis, San Francisco.....	(Jul)	98
Schiro, Frank, Sacramento.....	(Jul)	100
Schrier, Robert W., San Francisco.....	(Sep)	28
Schubert, James J., Sacramento.....	(Jul)	100
Schwartz, Donald A., Los Angeles.....	(Dec)	10
Scribner, Belding H., Seattle.....	(Sep)	57
Selzer, Arthur, San Francisco.....	(Nov)	1
Sherman, Samuel R., San Francisco.....	(Aug)	80
Shipper, John C., Sylmar.....	(Oct)	75
Simmons, Charles R., Loma Linda.....	(Dec)	4
Smartt, Walter H., Los Angeles.....	(Aug)	11, 32
Smith, Geoffrey A., Davis.....	(Jul)	96
Smith, Louis L., Loma Linda.....	(Dec)	4
Stamey, Thomas A., Stanford.....	(Jul)	1
Suryanarayana, B. V., Long Beach.....	(Sep)	16

T

Taichert, Louise C., San Francisco.....	(Aug)	11
Tashiro, M., Berkeley.....	(Jul)	28
Timothy, Mary, Stanford.....	(Jul)	1
Todd, Malcolm C., Long Beach.....	(Oct)	58
Turner, Jerrold A., Torrance.....	(Aug)	47

U

Ungerleider, J. Thomas, Los Angeles.....	(Sep)	38
--	-------	----

V

VanderLaan, W. P., La Jolla.....	(Aug)	38
Veith, Ilza, San Francisco.....	(Sep)	78
Vijayan, Nazhiyath, Davis.....	(Feb)	16
Vogel, John M., San Francisco.....	(Oct)	55

W

Ward, Paul H., Los Angeles.....	(Sep)	67
Weiss, Audrey T., Santa Ana.....	(Dec)	10
Wilkins, Jeanette, Los Angeles.....	(Nov)	16

Y

Yedidia, Avram, Berkeley.....	(Oct)	69
Young, Joe, San Diego.....	(Oct)	24

Z

Zimmerman, Murray C., Whittier.....	(Nov)	64
-------------------------------------	-------	----

IN MEMORIAM

Abbett, Arthur Louis, April 4, 1971.....	(Jul)	110
Adelstein, Lco Joel, Jul 31, 1971.....	(Oct)	82
Aker, Cecil G., Jul 10, 1971.....	(Sep)	96
Alden, Ward Clair, Jul 22, 1971.....	(Oct)	82
Allen, Warren Barrett, Sep 11, 1971.....	(Nov)	81

Andonian, Andon Armand, Sep 15, 1971....	(Nov)	81
Arnoff, William Harry, Oct 9, 1971.....	(Dec)	94
Ayers, Robert L., Mar 17, 1971.....	(Dec)	94
Benson, Clarence, Oct 22, 1971.....	(Dec)	94
Berg, Robert W., Jul 4, 1971.....	(Sep)	96

Bisel, Jerald Nathaniel, Sep 28, 1971.....(Nov)	81	Martin, Jerry Gene, May 8, 1971.....(Jul)	110
Blossom, Robert Alden, Aug 24, 1971.....(Nov)	81	Martine, Paul Henry, Mar 8, 1971.....(Dec)	95
Bolender, Melvin C., May 23, 1971.....(Aug)	97	Maurer, Robert D., Aug 28, 1971.....(Nov)	82
Bradbury, William C., Sep 15, 1971.....(Nov)	81	McCowin, Joseph Aaron, Jan 4, 1971.....(Aug)	97
Brifman, Theodore, Oct 11, 1971.....(Dec)	94	McGovern, Bernard E., Apr 30, 1971.....(Jul)	110
Brophy, John R., Jul 29, 1971.....(Oct)	82	Merritt, Robert Edward, Jun 23, 1971.....(Aug)	97
Burge, Martin Harless, Jul 21, 1971.....(Sep)	96	Meyer, Hans A., Jul 30, 1971.....(Nov)	82
Cantu, Jaime Teofilo, Sep 22, 1971.....(Nov)	81	Michael, Paul P. E., Aug 3, 1971.....(Oct)	82
Carlisle, Paul W., Oct 12, 1971.....(Dec)	94	Milholland, William George, May 8, 1971.....(Jul)	110
Carlson, Clifford M., Aug 20, 1971.....(Oct)	82	Miller, Frederick C., Aug 7, 1971.....(Oct)	82
Carlson, Edvard A., Oct 13, 1971.....(Dec)	94	Mills, Stephen Roy, May 6, 1971.....(Jul)	110
Carman, Henry F., Jr., Aug 11, 1971.....(Oct)	82	Mullenix, Ralph B., Oct 8, 1971.....(Dec)	95
Christierson, Sigurd von, Jun 29, 1971.....(Sep)	96	Newman, John Wilson, Aug 31, 1971.....(Nov)	82
Coleman, Harold S., Oct 12, 1971.....(Dec)	94	Newman, Howard, Sep 7, 1971.....(Nov)	82
Cornelius, Lawrence R., Sep 4, 1971.....(Nov)	81	Nicola, Tesla Case, Mar 15, 1971.....(Jul)	110
Dalton, Eric G., Sep 15, 1971.....(Dec)	94	Nolan, Frank Gregory, May 22, 1971.....(Jul)	110
Demandante, Primitiva D., Jun 6, 1971.....(Aug)	97	Nunn, William Evans, Oct 8, 1971.....(Dec)	95
Dow, Julian Neal, Jun 6, 1971.....(Aug)	97	Olsen, Sidney, Apr 21, 1971.....(Jul)	110
Eckerle, William Joseph, Jul 11, 1971.....(Oct)	82	Parham, Beverly Blunt, Feb 13, 1971.....(Jul)	110
Eckert, John Ross, Jul 31, 1971.....(Oct)	82	Peterson, Carl Andrew, Jul 8, 1971.....(Sep)	96
Emery, Claude E., May 25, 1971.....(Jul)	110	Peterson, Joseph B., Sep 13, 1971.....(Nov)	82
Fairchild, Gordon E., Jun 16, 1971.....(Sep)	96	Pimentel, George Brazil, Apr 16, 1971.....(Jul)	110
Farrand, Roderick C., Apr 17.....(Aug)	97	Piness, George, Dec 26, 1970.....(Jul)	110
Firestone, George M., Oct 18, 1971.....(Dec)	94	Pohlman, Max Edward, Jul 31, 1971.....(Oct)	82
Foster, Harry Emerson, Jun 26, 1971.....(Aug)	97	Robbins, Arthur C., Jr., Aug 8, 1971.....(Oct)	82
Franklin, Charles Thomas, Aug 27, 1971.....(Nov)	81	Roe, Harold Ewart, Apr 23, 1971.....(Jul)	110
Gonzales, Florentino A., Oct 16, 1971.....(Dec)	94	Rohlfes, Bernhard Joseph, Oct 16, 1971.....(Dec)	95
Goosenberg, Jerry, Jun 13, 1971.....(Aug)	97	Ruth, Edward Samuel, Jul 8, 1971.....(Sep)	96
Gordon, Asher T., Jun 12, 1971.....(Aug)	97	Ryan, Albert Freeman, Dec 4, 1970.....(Sep)	96
Gourley, Ina, Sep 21, 1971.....(Nov)	81	Salvater, Max L., Jul 12, 1971.....(Sep)	96
Gray, Percival A., Jr., May 16, 1971.....(Jul)	110	Samuels, Julius Lewis, Sep 13, 1971.....(Nov)	82
Greening, Paul King, Jun 17, 1971.....(Aug)	97	Schmidt, Hans, Aug 27, 1971.....(Nov)	82
Haas, Sylvan Lewis, Jun 21, 1971.....(Aug)	97	Schwartz, Herbert Perry, Oct 2, 1971.....(Dec)	95
Hebard, Floyd Malcolm, May 22, 1971.....(Aug)	97	Sebastian, Charles Francis, Sep 3, 1971.....(Nov)	82
Hill, Jack C., Sep 11, 1971.....(Nov)	81	Shaw, Lysle Orting, Sep 21, 1971.....(Dec)	95
Hirschfeld, Mervyn H., Jul 5, 1971.....(Sep)	96	Sheldon, Eberle C., Sep 10, 1971.....(Nov)	82
Howard, Wayne Cox, Sep 22, 1971.....(Nov)	81	Shropshire, Lee, Dec 17, 1970.....(Jul)	110
Howson, Carl Robert, Sep 29, 1971.....(Dec)	94	Singman, David, May 5, 1971.....(Jul)	110
Johnson, James Knox, Aug 6, 1971.....(Oct)	82	Sipple, Ledley M., Jan 3, 1971.....(Jul)	110
Kaffesieder, Lewis I., Oct 26, 1971.....(Dec)	94	Smith, Dale Hancock, Aug 19, 1971.....(Nov)	82
Knorp, William Frederick, Sep 24, 1971.....(Nov)	81	Snow, Rodney H., Sep 28, 1971.....(Nov)	82
Kolts, Robert F., Aug 1971.....(Nov)	81	Stephenson, Henry A., Oct 19, 1971.....(Dec)	95
Kulchar, George V., Jul 11, 1971.....(Sep)	96	Stephl, Paul David, Sep 28, 1971.....(Dec)	95
Lane, Arthur R., Oct 16, 1971.....(Dec)	94	Strouse, Carl David, Aug 25, 1971.....(Nov)	82
Leary, James Jeremiah, Jr., Oct 25, 1971.....(Dec)	94	Thompson, Roland Lewis, Dec 23, 1970.....(Aug)	97
Lindsay, Charles V., Sr., Oct 14, 1971.....(Dec)	95	Todd, Max A., Sep 28, 1971.....(Dec)	95
Littlefield, Don Claude, Jul 30, 1971.....(Nov)	82	Vail, James B., Jul 31, 1971.....(Oct)	82
Liu, David C. (Ching T.), Aug 4, 1971.....(Oct)	82	Van de Carr, Francis Rene, Sr., Jun 6, 1971.....(Aug)	97
Loewenstein, Wilhelmmina, Aug 1, 1971.....(Oct)	82	von Dessonneck, Emil S., Jul 8, 1971.....(Sep)	96
Ludvig, Charles H., Apr 30, 1971.....(Jul)	110	Winfield, Mark Edwin, Jun 3, 1971.....(Aug)	97
MacDonald, William Hugh, Oct 8, 1971.....(Dec)	95	Woods, Neal Chaffee, Sr., May 16, 1971.....(Aug)	97
Madden, Donald Joseph, Aug 13, 1971.....(Nov)	82	Wyne, Paul Samuel, Aug 13, 1971.....(Oct)	82
Marshall, Irving Arthur, Sep 30, 1971.....(Dec)	95	Yaw, Louis R., Jul 7, 1971.....(Sep)	96

SUBJECT INDEX

A	
Abortion, see <i>Therapeutic</i>	
Acid, Amino, Metabolism, see <i>Disorders</i>	
Acute Renal Failure—Diagnosis, Management and Pathogenesis (Medical Staff Conference).....(Sep)	28
Editorial, Leonard J. Quadracci and Belding H. Scribner.....(Sep)	57
ad hoc Committee to Study California Blue Shield/CMA Relationships, see <i>California Blue Shield</i>	
Addiction, Heroin, see <i>Medical Complications</i>	
Addicts, Narcotic, see <i>Malaria Transmission</i>	
Air Pollution, Health Effects and Urban Growth, Louis F. Saylor.....(Jul)	106
Letter to Editor, Clifford L. Graves.....(Sep)	73
Alaska, see <i>Survey</i>	
Albumin, Serum, see <i>Aseptic Meningitis</i>	
Allergy, Important Advances in, see <i>Epitomes</i>	
Allograft Rejection, see <i>Renal</i>	
AMA Constitutional Convention (Editorial).....(Oct)	50
AMA Convention—A Report on Activities by the CMA Delegation, Samuel R. Sherman.....(Aug)	80

Amendments, see <i>Proposed</i>	
AMA [Membership], see <i>Question</i>	
Amino Acid Metabolism, see <i>Disorders</i>	
Anemia and Heart Failure—Association with Cardiomyopathy and Multiple Blood Transfusions (Medical Staff Conference) (Aug)	61
Antigen, Australia, see <i>Maternal and Neonatal</i>	
Approach to Diagnosis and Treatment of Herpes Simplex Encephalitis—A Report of Two Cases, Marc J. Gurwith, Charles E. Harman and Thomas C. Merigan (Dec)	62
Arteriography, see <i>Coronary</i>	
Arteriography, Coronary, see <i>Indications for</i>	
Arteritis, see <i>Giant Cell</i>	
Ascites, see <i>Hemorrhagic</i>	
Aseptic Meningitis Following Intrathecal Radioiodinated Serum Albumin, Borina Drinov and Richard Dubou (Sep)	64
Asian Flu, see <i>Fingernail Furrows</i>	
Aspirin-Induced Prolongation of the Ivy Bleeding Time—Its Diagnostic Usefulness, Mervyn A. Sahud and Richard J. Cohen (Oct)	10
Australia Antigen, see <i>Maternal</i>	
B	
[Bacteria, Intestinal], see <i>Recurrent Urinary Infections</i>	
(Beau's Lines), see <i>Fingernail Furrows</i>	
Biologic Premise (Editorial) (Sep)	56
[Biomedical Library], see <i>Pacific Southwest</i>	
Bleeding Time, see <i>Aspirin-Induced</i>	
Blunt Laryngotracheal Trauma, Bruce W. Jafek, R. Melvin Butler and Paul H. Ward (Sep)	67
Blue Shield, see <i>California</i>	
Blue Shield, see <i>Present and Future Role</i>	
Blood Transfusions, see <i>Anemia</i>	
Book Reviews:	
American Medicine in Crisis, <i>Luongo</i> (Oct)	83
Bleeding Problems in Clinical Medicine, <i>Quick</i> (Oct)	85
Cardiovascular Dynamics—3rd Ed., <i>Rushmer</i> (Oct)	83
Clinical Recognition of Congenital Heart Disease, The, <i>Perloff</i> (Oct)	84
Congenital and Pediatric Glaucomas, <i>Shaffer & Weiss</i> (Aug)	98
Current Dermatologic Management, <i>Maddin</i> (Oct)	86
Founders of Neurology, The—2nd Ed., <i>Haymaker & Schiller</i> (Oct)	84
Ophthalmic Plastic Surgery—4th Ed., <i>Fox</i> (Aug)	98
Overcoming the Fear of Death, <i>Gordon</i> (Oct)	85
Reconstructive Surgery of the Middle Ear, <i>Wolferman</i> (Aug)	98
Synopsis of Pharmacology, A—2nd Ed., <i>Sutherland</i> (Oct)	83
Tumours of the Testicle, <i>Blandy et al.</i> (Oct)	84
Urological Surgery—4th Ed., <i>Dodson</i> (Oct)	86
Bush Country, see Practice of Medicine	
C	
California, see <i>Therapeutic Abortions</i>	
California Blue Shield, see <i>Present and Future Role</i>	
California Blue Shield/CMA Relationships—Conclusions and Recommendations of the ad hoc Committee—Final Report to House of Delegates (Dec)	88
California Medical Association:	
AMA Convention—A Report on Activities by the CMA Delegation, Samuel R. Sherman (Aug)	80
California Blue Shield/CMA Relationships—Conclusions and Recommendations of the ad hoc Committee—Final Report to House of Delegates (Dec)	88
Proposed CMA Constitutional Amendments for Action in 1972 (Nov)	77
(Dec) Annual Session Program Page 30	
Question: Shall Organized Medicine Be Unified, or Separate? (Jul)	81
Structural Relationship of AMA, CMA and Component Societies, Howard Hassard (Jul)	82
Statements for Unified, for Separate (Jul)	83
(Aug)	82
Editorial (Aug)	77
California State Plan for Health—A Critique (Editorial), Malcolm C. Todd (Oct)	53
California Tumor Registry, see <i>Cancer of the Pancreas</i>	
Cancer of the Pancreas in California, 1942-1967—The California Tumor Registry Experience, Lawrence Stirling Krain (Jul)	38
Cardiomyopathy, see <i>Anemia</i>	
Carotid Endarterectomy, see <i>Safe Approach</i>	
Catheter Fragments, see <i>Retrieval</i>	
Certified Hospital Admission Program [Sacramento County Medical Society Medical Care Foundation], James J. Schubert, James Bramham, Frank Schiro, and H. John Rush (Jul)	100
Changing Concepts on the Control of Growth Hormone Secretion in Man, W. P. VanderLaan (Aug)	38
Editorial, David L. Rimoin (Aug)	75
[CHAP] see <i>Certified Hospital Admission Program</i>	
Childhood Encopresis—A Neurodevelopmental-Family Approach to Management, Louise C. Tachert (Aug)	11
Children, see <i>Congenital Heart</i>	
Chlorpropamide, see <i>Oral Therapy of Diabetes Insipidus</i>	
Circulation, see <i>Extracorporeal</i>	
Circumcision Device, see <i>New</i>	
[Citizen's Board of Inquiry], see <i>"Heal Yourself"</i>	
Clinical Cardiology:	
Congenital Heart Disease in the First Year of Life, Sidney Blumenthal and Mary Jane Jesse (Jul)	108
Congenital Heart Disease in Children, Sidney Blumenthal and Mary Jane Jesse (Sep)	91
Extracorporeal Circulation—Part I & II, Robert S. Litwak (Oct)	80
(Nov)	79
[Clinic, Obstetrics and Gynecology], see <i>Excellence Need Not Cost More</i>	
Clinical Note:	
Fingernail Furrows (Beau's Lines) as a Retrospective Index of the Severity of Asian Flu in 1968-69, Nicholas L. Petrakis and Asa G. Churchill (Dec)	77
Clinical Research, see Phenylketonuria	
CMA Committee on the Role of Medicine in Society, Medical Student Representatives, Report on Student Participation in Organized Medicine (Jul)	96
CMA [Membership], see <i>Question</i>	
College Health Services, see <i>Community</i>	
College Health Services (Editorial), Henry B. Bruyn (Nov)	51
Community College Health Services—A Health Care Crisis, E. D. Lovett (Nov)	66
Editorial, Henry B. Bruyn (Nov)	51

Complication of Smallpox Vaccination, 1968—Results of a Statewide Survey in Alaska, Paul S. Clark and J. Michael Lane.....(Sep)	7
Component Societies [Membership], see <i>Question</i>	
Computerized Entry into Medical Care—Its Impact on Doctor-Patient Relationships (Health Care Team), Avram Yedidia, M. A. Bunow, and Michael S. Muldavin.....(Oct)	69
Congenital Heart Disease in Children, Sidney Blumenthal and Mary Jane Jesse.....(Sep)	91
Congenital Heart Disease in the First Year of Life, Sidney Blumenthal and Mary Jane Jesse....(Jul)	108
Conserving California's Water, Louis F. Saylor (Nov)	75
Constitutional Amendments, see <i>Proposed</i>	
Constitutional Convention, see <i>AMA</i>	
Contact Lenses [Plastic], see <i>Soft</i>	
Contracture of the Fingers, see <i>Dupuytren's</i>	
Contributors to CALIFORNIA MEDICINE, 1971. (Dec)	91
Control of Growth Hormone Secretion, see <i>Changing Concepts</i>	
Controversial Issue:	
Doctor and Sex Education, The, Joshua S. Golden and Cole Mason.....(Oct)	60
<hr/>	
Coronary Arteriography, see <i>Indications for</i>	
Coronary Arteriography: Where? When? (Editorial), Herbert E. Griswold and Donald G. Kassebaum.....(Nov)	52
Correction of Statement Regarding Thioridazine [UC Fall Symposium on Obstetrics and Gynecology], see <i>Iatrogenic Embryonic Defects</i>	
Costs, Health Care, see <i>On Cutting</i>	
Current Concepts in the Treatment of Hypertension (Medical Staff Conference).....(Jul)	58
Cutting Costs, see <i>On Cutting</i>	
<hr/>	
D	
Dealing in Futures (Editorial):	
Part I—Medicine and Health Care.....(Jul)	79
Part II—In Democratic Societies.....(Aug)	77
Part III—Planning in CMA.....(Sep)	59
Delegation, CMA, see <i>AMA Convention</i>	
Democratic Societies, see <i>Dealing in Futures</i>	
Dermatologic Radiotherapy—R.I.P., Ervin Epstein.....(Nov)	7
Diabetes Insipidus, see <i>Oral Therapy of</i>	
Diabetes Mellitus, see <i>Myocardial Infarction</i>	
Diagnosis, see <i>Acute Renal Failure</i>	
Diatrizoate, see <i>Myelography</i>	
Diazepam, see <i>Tetanus</i>	
Disease, Imported, see <i>Malaria</i>	
Diseases, Respiratory, see <i>Evaluation of the Role of Nitrogen Dioxide</i>	
Disorders of Amino Acid Metabolism—1971, John H. Menkes.....(Oct)	14
Editorial, William L. Nyhan.....(Oct)	57
DOA for the AMA and CMA [Voluntary vs. Compulsory] (Letter to the Editor), John E. Kirkpatrick.....(Sep)	72
Doctor and the "Doper," J. Thomas Ungerleider.....(Sep)	38
Doctor and Sex Education, The,—A Controversial Issue, Joshua S. Golden and Cole Mason....(Oct)	60
Doctor-Patient Relationships, see <i>Computerized</i>	
"Doper" The, see <i>Doctor and</i>	
[Drug Form], see <i>Hot Word from #AB 3,522,477</i>	
Duodenocolic Fistula, Harrison J. Kornfield and Richard A. Hogan.....(Nov)	58

Dupuytren's Contracture of the Fingers—A Simplified Approach to the Surgical Treatment, Richard I. Gonzalez.....(Aug)	25
Dwarf, Pituitary, see <i>Treatment with Human Growth Hormone</i>	

E

Earthquake Under Grass [Marijuana] (Letter to Editor), John C. Shipper.....(Oct)	75
--	----

Editorials:

Acute Renal Failure: Prevention, Prophylaxis and Progress, Leonard J. Quadracci and Belding H. Scribner.....(Sep)	57
AMA Constitutional Convention.....(Oct)	50
Biologic Premise.....(Sep)	56
California State Plan for Health—A Critique..(Oct)	53
College Health Services, Henry B. Bruyn....(Nov)	51
Coronary Arteriography: Where? When?, Herbert E. Griswold and Donald G. Kassebaum.....(Nov)	52
Dealing in Futures:	
Part I—In Medicine and Health Care.....(Jul)	79
Part II—In Democratic Societies.....(Aug)	77
Part III—Planning in CMA.....(Sep)	59
Happy Choice, A [John R. Hogness, President of New National Institute of Medicine].....(Aug)	79
Health Care Team, The.....(Nov)	54
Inborn Errors of Metabolism, William L. Nyhan.....(Oct)	52
Marine Pollution and Human Health, Bruce W. Halstead.....(Dec)	61
Medical Education in Transformation.....(Nov)	53
National Health Insurance— <i>Caveat Emptor</i> ..(Dec)	55
Nephrotic Syndrome, The, Arnold S. Relman (Dec)	58
New Knowledge About HGH [Human Growth Hormone], David L. Rimoin.....(Aug)	75
Of Nurses and Physician's Assistants.....(Oct)	54
On Cutting Costs in Health Care.....(Jul)	75
One-hundred-first Scientific Assembly.....(Dec)	62
Ox, NO _x , PAN and SO _x : When and How Are They Toxic, John R. Goldsmith.....(Sep)	55
Phenylketonuria, The Inborn Errors of Metabolism, and Clinical Research—1971, Charles J. Epstein.....(Jul)	76
Renal Allograft Rejection, John P. Merrill....(Dec)	56
Tetanus—The Role of Diazepam in Therapy, John V. Bennett.....(Oct)	51
United or Separate?.....(Aug)	77
Venereal Disease Epidemic, Walter H. Smartt (Aug)	78
Letter to Editor, Erwin H. Braff.....(Oct)	75

Education, see *Medical*

Embryonic Defects, see *Iatrogenic*

Encephalitis, Herpes Simplex, see *Approach to Diagnosis*

Encopresis, see *Childhood*

Encounter Groups, see *Training Groups*

Enderectomy, Carotid, see *Safe Approach*

Endocarditis, Fungal, see *Spectrum of*

Enterobacteria, Intestinal, see *Recurrent Urinary Infections*

Epitomes of Progress in Clinical Medicine:

Pediatrics.....(Jul)	68
Radiology.....(Aug)	65
Psychiatry and Neurology.....(Sep)	41
Allergy.....(Oct)	41
General and Family Practice.....(Dec)	48

Evaluation of Renal Vascular Hypertension and Primary Hyperaldosteronism (Medical Staff Conference) (Dec)	40	"Heal Yourself" [Dissenting Opinion of Report of Citizens Board of Inquiry into Health Services for Americans], Gerald Besson..... (Dec)	79
Evaluation of the Role of Nitrogen Dioxide in the Development of Respiratory Diseases in Man, Elliot Goldstein (Sep)	21	Health, see <i>Air Pollution</i>	
Editorial, John R. Goldsmith..... (Sep)	55	Health Care, see <i>Dealing in Futures</i>	
Excellence Need Not Cost More—Relating a Free Clinic's Services to the Patient's Convenience and Feelings (Health Care Team), Leonard M. Parker (Nov)	72	Health Care, see <i>On Cutting Costs</i>	
Extracorporeal Circulation—Part I & Part II, Robert S. Litwak..... (Oct)	80	Health Care Crisis, see <i>Community</i>	
..... (Nov)	79	Health Care Team, The (Editorial)..... (Nov)	54
F		Health Care Team:	
Family and General Practice, Important Advances in, see <i>Epitomes</i>		Computerized Entry into Medical Care—Its Impact on Doctor-Patient Relationships, Avram Yedidia, M. A. Bunow and Michael S. Muldavin.... (Oct)	69
Fingernail Furrows (Beau's Lines) as a Retrospective Index of the Severity of Asian flu in 1968-69 (Clinical Note), Nicholas L. Petrakis and Asa G. Churchill (Dec)	77	Excellence Need Not Cost More—Relating a Free Clinic's Services to the Patient's Convenience and Feelings, Leonard M. Parker..... (Nov)	72
Fingers, see <i>Dupuytren's Contracture of</i>			
Fistula, see <i>Duodenocolic</i>		Health, Human, see <i>Marine Pollution</i>	
Flu, Asian, see <i>Fingernail Furrows</i>		Health Insurance, see <i>National</i>	
Frederick the Great, see <i>Medical World of</i>		Health Plan, see <i>California</i>	
Free Clinic's Services, see <i>Excellence Need Not Cost More</i>		Health Service, see <i>College</i>	
Frontiers of Psychiatry and Medicine:		Health Services, see <i>Community</i>	
New Methods of Psychiatric Treatment, Don E. Flinn (Jul)	88	[Health Services for Americans], see "Heal Yourself"	
Training Groups, Encounter Groups, Sensitivity Groups and Group Psychotherapy, Louis A. Gottschalk, E. Mansell Pattison and Donald W. Schafer (Aug)	87	Health Testing, see <i>Multiphasic</i>	
Doctor and the "Doper," The, J. Thomas Ungerleider (Sep)	38	Heart Disease, see <i>Congenital</i>	
Functional Aspects of the Rejection of Transplanted Kidneys, W. J. Dempster..... (Dec)	17	Heart Failure, see <i>Anemia</i>	
Editorial, John P. Merrill..... (Dec)	56	Hemorrhagic Ascites: An Unusual Complication of Multiple Myeloma, James L. Poth and Ralph P. George (Sep)	61
Fungal Endocarditis, see <i>Spectrum of</i>		Heroin Addiction, see <i>Medical Complications</i>	
Futures, see <i>Dealing in</i>		Herpes Simplex Encephalitis [Treated with Iodo-deoxyuridine (IDUR)], see <i>Approach to Diagnosis</i>	
G		HGH [Human Growth Hormone], see <i>Changing Concepts, New Knowledge of, and Treatment with Human Growth Hormone</i>	
General and Family Practice, Important Advances in, see <i>Epitomes</i>		[Hogness, John R.], see <i>A Happy Choice</i>	
Ghana, see <i>Practice of Medicine</i>		Hormone, Human Growth, see <i>Treatment with</i>	
Giant Cell Arteritis with Myositis and Myocarditis, L. James Kennedy, Jr., and M. J. Mitchinson... (Jul)	84	Hormone Secretion, Growth, see <i>Changing Concepts, and New Knowledge</i>	
[Gonorrhea], see <i>Venereal Disease</i>		Hospital Admission Program, see <i>Certified</i>	
Gonorrhea Today—Problems of Diagnosis, Management, Treatment, R. C. Reznichuk, W. H. Smartt and S. A. Brosman..... (Aug)	32	Hospitalization, Psychiatric, see <i>Involuntary</i>	
Government and Medicine:		Hot Word from #AB 3,522,477 (Letter to Editor), William Baxter..... (Sep)	72
Pacific Southwest Regional Medical Library Service UC, LA Biomedical Library, Nelson J. Gilman (Oct)	67	House of Delegates, see <i>California Blue Shield/CMA Relationships</i>	
Grass, see <i>Earthquake Under</i>		Human Health, see <i>Marine Pollution</i>	
Group Psychotherapy, see <i>Training Groups</i>		[Human Growth Hormone (HGH)], see <i>Changing Concepts, New Knowledge, and Treatment with Hypaque®</i> , Inadvertent Use, see <i>Myelography</i>	
Growth Hormone, see <i>Changing Concepts</i>		Hyperaldosteronism, see <i>Evaluation of Renal Vascular Hypertension</i>	
Growth Hormone (Li), see <i>Treatment with</i>		Hypercalcemia, see <i>Mithramycin</i>	
H		Hypertension, see <i>Current Concepts and Evaluation of Renal Vascular</i>	
Happy Choice, A [John R. Hogness, President of New National Institute of Medicine] (Editorial) (Aug)	79	[Hyperthyroidism], see <i>Thyroid Storm</i>	
Harbor General Hospital, and UC, Los Angeles, see <i>Specialty Conferences</i>		I	
		Iatrogenic Embryonic Defects—Correction of Statement Regarding Thioridazine [UC Fall Symposium on Obstetrics and Gynecology] (Letter to Editor), Ian W. Monie..... (Jul)	99
		Important Advances in Clinical Medicine, see <i>Epitomes</i>	
		In the Forefront:	
		Certified Hospital Admission Program, James J. Schubert, James Bramham, Frank Schiro, and H. John Rush (Jul)	100

Physicians' Benevolence Fund, Clyde L. Boice(Dec)	86	Report on Student Participation in Organized Medicine (Prepared by Medical Student Representatives on the CMA Committee on the Role of Medicine in Society), William J. Nowack, Geoffrey A. Smith, Paul Barrett, Larry Freeman, and Peter Libby	(Jul)	96
Inborn Errors, see <i>Phenylketonuria</i>		Synergistic Danger in Ketamine and Innovar®, Edward R. Bloomquist.....	(Nov)	64
Inborn Errors of Metabolism (Editorial), William L. Nyhan	(Oct)	52		
Indications for Coronary Arteriography—Risks vs. Benefits, Arthur Selzer, William L. Anderson and Harold W. March.....	(Nov)	1		
Editorial, Herbert E. Griswold and Donald G. Kassebaum	(Nov)	52		
[Infants], see <i>Congenital Heart Disease in First Year of Life</i>				
Infectious Disease, see <i>Syphilis</i>				
Infections, Urinary, see <i>Recurrent</i>				
Information:				
Cardiology articles, see <i>Clinical Cardiology</i>				
Selective Service System and Physicians, L. S. Goerke	(Aug)	94		
Some Aspects of Medical Practice at UCLA, C. G. Craddock	(Sep)	89		
Innovar®, see <i>Synergistic Danger</i>				
Insurance, see <i>National</i>				
[Intestinal Bacteria], see <i>Recurrent Urinary Infections</i>				
Intrathecal Radioiodinated Serum Albumin, see <i>Aseptic Meningitis</i>				
Intestinal Enterobacteria, see <i>Recurrent Urinary Infections</i>				
Involuntary Psychiatric Hospitalization [Lanternman-Petris-Short Act], Donald A. Schwartz and Audrey T. Weiss	(Dec)	10		
[Iododeoxyuridine (IDU)] Therapy of Herpes Simplex Encephalitis, see <i>Approach to Diagnosis</i>				
Isotope Evaluation of Splenic Size in Hereditary Spherocytosis, Dale A. Bergeron and John M. Vogel	(Oct)	55		
Ivy Bleeding Time, see <i>Aspirin-Induced</i>				
K				
[Ketaject®], see <i>Synergistic Danger</i>				
[Ketalar®], see <i>Synergistic Danger</i>				
Kidneys, see <i>Functional Aspects</i>				
L				
[Lanternman-Petris-Short Act], see <i>Involuntary Psychiatric Hospitalization</i>				
Laryngotracheal Trauma, see <i>Blunt</i>				
Lenses, see <i>Soft Contact</i>				
Letters to Editor:				
Air Pollution, Health Effects and Urban Growth, Clifford L. Graves.....	(Sep)	73		
DOA for the AMA and CMA [Voluntary vs. Compulsory Membership], John E. Kirkpatrick	(Sep)	72		
Earthquake Under Grass [Marijuana], John C. Shipper	(Oct)	75		
Hot Word from #AB 3,522,477 [Narcotics Form], William Baxter.....	(Sep)	72		
Iatrogenic Embryonic Defects—Correction of Statement Regarding Thioridazine [UC Fall Symposium on Obstetrics and Gynecology], Ian W. Monie	(Jul)	99		
Magendie on Medicine, Francis Schiller.....	(Jul)	98		
Penicillin Reactions, Murray C. Zimmerman.....	(Nov)	64		
"Pharmacist and the Physician," Donald W. Petit	(Jul)	96		
Progonasyl for VD Prophylaxis?, Erwin H. Braff	(Oct)	75		
Library Service, see <i>Pacific Southwest</i>				
[Lockjaw], see <i>Tetanus</i>				
M				
Magendie on Medicine (Letter to Editor), Francis Schiller	(Jul)	98		
Malaria—An "Imported" Disease to Be Reckoned with in the U. S., Elizabeth Barrett-Connor.....	(Aug)	24		
Malaria Transmission Among Narcotic Addicts — A Report of Ten Cases and Review of the Literature, Rodger L. Bick and James E. Anhalt, Jr.	(Nov)	56		
Malignancy, see <i>Mithramycin</i>				
[Maple Syrup Disease], see <i>Disorders of Amino Acid Metabolism</i>				
Marine Pollution and Human Health (Editorial), Bruce W. Halstead.....	(Dec)	61		
[Marijuana], see <i>Earthquake Under Grass</i>				
Marijuana Use, see <i>Personality Factors</i>				
Maternal and Neonatal Australia Antigen, Thomas F. Keys, Calvin J. Hobel, Susan Ritman, William Oh, Gary L. Gitnick and William L. Hewitt	(Dec)	1		
Medical Care, see <i>Computerized Entry</i>				
Medical Care Foundation, Sacramento County Medical Society, see <i>Certified Hospital Admission Program</i>				
Medical Complications of Heroin Addiction (Medical Staff Conference).....	(Nov)	42		
Medical Education in Transformation (Editorial)	(Nov)	53		
Medical Library UC,LA, see <i>Pacific Southwest</i>				
Medical Practice, see <i>Some Aspects</i>				
Medical Progress:				
Phenylketonuria and Its Variations — A Review of Recent Developments, Milan E. Blaskovics and Thomas L. Nelson.....	(Jul)	42		
Editorial, Charles J. Epstein.....	(Jul)	76		
Changing Concepts on the Control of Growth Hormone Secretion in Man, W. P. VanderLaan (Aug) Editorial, David L. Rimoin.....	(Aug)	38		75
Evaluation of the Role of Nitrogen Dioxide in the Development of Respiratory Diseases in Man, Elliot Goldstein.....	(Sep)	21		
Editorial, John R. Goldsmith.....	(Sep)	55		
Disorders of Amino Acid Metabolism—1971, John N. Menkes	(Oct)	14		
Editorial, William L. Nyhan.....	(Oct)	52		
Functional Aspects of the Rejection of Transplanted Kidneys, W. J. Dempster.....	(Dec)	17		
Editorial, John P. Merrill.....	(Dec)	56		
Medical Staff Conferences:				
Current Concepts in the Treatment of Hypertension, Chief Discussant: Kenneth L. Melmon.....	(Jul)	58		
Anemia and Heart Failure—Association with Cardiomyopathy and Multiple Blood Transfusions, Chief Discussant: Celia Oakley.....	(Aug)	61		

Acute Renal Failure—Diagnosis, Management and Pathogenesis, Chief Discussant: Robert W. Sehrier (Sep)	28
Editorial, Leonard J. Quadraeci and Belding H. Seribner (Sep)	57
Spectrum of Fungal Endocarditis, The, Chief Discussant: David J. Drutz (Oct)	34
Medical Complications of Heroin Addiction, Chief Discussant: Charles E. Becker (Nov)	42
Evaluation of Renal Vascular Hypertension and Primary Hyperaldosteronism, Chief Discussant: Edward G. Biglieri (Dec)	40

Medical Student Representatives, see <i>Report on Student Participation in Organized Medicine</i>	
Medical World of Frederick the Great, The, Ilza Veith (Sep)	78
Medicine, see <i>Dealing in Futures</i>	
Medicine, see <i>Magendie</i>	
Medicine, see <i>Practice of</i>	
Medical, Clinical, Important Advances, see <i>Epitomes</i>	
[Medicine, National Institute of], see <i>A Happy Choice</i>	
Medicine, Organized, see <i>Question</i>	
Medicine, Organized, see <i>Report on Student Participation</i>	

Medicine in Perspective:

Practice of Medicine in the Bush Country of Ghana, Marlene E. Long (Jul)	102
Medical World of Frederick the Great, The, Ilza Veith (Sep)	78

Membership [in CMA and AMA], see <i>Question</i>	
[Membership Poll], see <i>United or Separate?</i>	
Meningitis, see <i>Aseptic</i>	
Metabolism, see <i>Disorders</i>	
Metabolism, see <i>Phenylketonuria</i>	
Metabolism, Carbohydrate, see <i>Myocardial Infarction</i>	
Mithramycin for Hypercalcemia of Malignancy, Thomas E. Godfrey (Oct)	1
Multiphasic Health Testing in the Clinic Setting, Joseph LaDon (Jul)	34
Myelography with Sodium Diatrizoate (Hypaque®)—Report of a Case of Inadvertent Use Complicated by Acute Renal Failure, Carroll M. Martin . . (Oct)	57
Myeloma, Multiple, see <i>Hemorrhagic Ascites</i>	
Myocardial Infarction and Carbohydrate Metabolism Relating to Diabetes Mellitus, Wilbert S. Aronow, B. V. Suryanarayana, and John R. Kent . . . (Sep)	16
Myocarditis, see <i>Giant Cell Arteritis</i>	
Myositis, see <i>Giant Cell Arteritis</i>	

N

Narcotic Addicts, see <i>Malaria Transmission</i>	
[Narcotics Form], see <i>Hot Word From</i>	
#AB3,522,477	
National Health Insurance— <i>Caveat Emptor</i> (Editorial) (Dec)	55
[National Institute of Medicine], see <i>A Happy Choice</i>	
Neonatal Australia Antigen, see <i>Maternal</i>	
Nephrotic Syndrome (UC, San Francisco, Medical Grand Rounds), Participants: Laurence E. Earley, Richard J. Havel, James Hopper, Jr., and Henry Grausz (Nov)	23
Editorial, Arnold S. Relman (Dec)	58
Neuralgia, Zoster and Postzoster, see <i>Triamcinolone-Procaïne in the Treatment of</i>	

Neurodevelopmental Approach, see <i>Childhood Encopresis</i>	
Neurology, Important Advances in, see <i>Epitomes</i>	
New Circumcision Device, A—A Preliminary Report, Lawrence D. Freeman (Aug)	24
New Knowledge About HGH [Human Growth Hormone] (Editorial), David L. Rimoin (Aug)	75
New Methods of Psychiatric Treatment, Don E. Flinn (Jul)	88
Nitrogen Dioxide, see <i>Evaluation of the Role of</i>	
Noise, The Fourth Pollution, Louis F. Saylor . . (Sep)	93
NO _x , see <i>Ox</i>	
Nurses and Physician's Assistants, Of (Editorial) (Oct)	54

O

[Obstetrics and Gynecology, uc Fall Symposium—Correction], see <i>Iatrogenic Embryonic Defects</i>	
[Obstetrics and Gynecology Clinic], see <i>Excellence</i>	
Need Not Cost More	
Of Nurses and Physician's Assistants (Editorial) (Oct)	54
On Cutting Costs in Health Care (Editorial) . . (Jul)	75
One-hundred-first Scientific Assembly (Editorial) (Dec)	62
Oral Therapy of Diabetes Insipidus with Chlorpropamide, William G. Cushard, Jr., Charles J. Beauchamp, and Neil D. Martin (Aug)	1
Organized Medicine, see <i>Report on Student Participation</i>	
Orthopedic Rehabilitation of the Stroke Patient, Richard Braun, Vert Mooney, Vernon L. Nickel, and Brian Roper (Nov)	11
Ox, NO _x , PAN and SO _x : When and How Are They Toxic (Editorial), John R. Goldsmith (Sep)	55

P

Pacific Southwest Regional Medical Library Service [UC, LA Biomedical Library], Nelson J. Gilman (Oct)	67
PAN, see <i>Ox</i>	
Pancreas, see <i>Cancer of the</i>	
Pathogenesis, see <i>Acute Renal Failure</i>	
Patient-Doctor Relationships, see <i>Computerized Entry into Medical Care</i>	
Pediatrics, Important Advances in, see <i>Epitomes</i>	
Penicillin Reactions (Letter to Editor), Murray C. Zimmerman (Nov)	64
Personality Factors Associated with Frequency of Marijuana Use, Evelyn Crumpton and Norman Q. Brill (Sep)	11
"Pharmacist and the Physician" (Letter to Editor), Donald W. Petit (Jul)	96
[Phenylketonuria], see <i>Disorders of Amino Acid Metabolism</i>	
Phenylketonuria, The Inborn Errors of Metabolism, and Clinical Research—1971, (Editorial), Charles J. Epstein (Jul)	76
Phenylketonuria and Its Variations—A Review of Recent Developments, Milan E. Blaskovics and Thomas L. Nelson (Jul)	42
Editorial, Charles J. Epstein (Jul)	76
Physician, see <i>Pharmacist</i>	
Physician's Assistants, see <i>Of Nurses and</i>	
Physicians' Benevolence Fund (In the Forefront), Clyde L. Boice (Dec)	86
Physicians, see <i>Selective Service System</i>	
Pituitary Dwarf, see <i>Treatment with Human Growth Hormone</i>	

[PKU], see <i>Disorders of Amino Acid Metabolism</i>	
[PKU], see <i>Phenylketonuria</i>	
Plan for Health, see <i>California</i>	
[Plastic] Contact Lenses, see <i>Soft</i>	
Pollution	
Pollution, see <i>Air</i>	
Pollution, see <i>Marine</i>	
Pollution, see <i>Noise</i>	
Postzoster and Zoster Neuralgia, see <i>Triamcinolone-Procaïne</i>	
Practice of Medicine in the Bush Country of Ghana, Marlene E. Long.....(Jul)	102
Premarital Examination for Syphilis, Louis F. Saylor.....(Oct)	78
Present and Future Role of Blue Shield, Carl E. Anderson.....(Sep)	74
Prevention, see <i>Acute Renal Failure</i>	
Progonasyl for VD Prophylaxis? (Letter to Editor), Erwin H. Braff.....(Oct)	75
Prophylaxis, see <i>Acute Renal Failure</i>	
Proposed CMA Constitutional Amendments for Action in 1972.....(Nov) 77, (Dec) Annual Session Program Page 30	
Psychiatric Hospitalization, see <i>Involuntary</i>	
Psychiatric Treatment, see <i>New Methods of</i>	
Psychiatry and Neurology, Important Advances in, see <i>Epitomes</i>	
Psychotherapy, see <i>Training Groups</i>	
Public Health Reports:	
Air Pollution, Health Effects and Urban Growth.....(Jul)	106
Letter to Editor, Clifford L. Graves.....(Sep)	73
Soft Contact Lenses.....(Aug)	96
Noise, The Fourth Pollution.....(Sep)	93
Premarital Examinations for Syphilis.....(Oct)	78
Conserving California's Water.....(Nov)	75

Q

Question: Shall Organized Medicine Be Unified, or Separate?.....(Jul)	81
Structural Relationship of AMA, CMA and Component Societies, Howard Hassard.....(Jul)	82
Statements for Unified, for Separate.....(Jul)	83
.....(Aug)	82
Editorial.....(Aug)	77

R

Radioiodinated Serum Albumin, see <i>Aseptic Meningitis</i>	
Radiology, Important Advances in, see <i>Epitomes</i>	
Radiotherapy, see <i>Dermatologic</i>	
Reactions, see <i>Penicillin</i>	
Recurrent Urinary Infections in Adult Women—The Role of Interoital Enterobacteria, Thomas A. Stamey, Mary Timothy, Marcia Millar and Gladys Mihara.....(Jul)	1
Registry, Tumor, see <i>Cancer of the Pancreas</i>	
Rehabilitation of the Stroke Patient, see <i>Orthopedic</i>	
Rejection of Transplanted Kidneys, see <i>Functional Aspects</i>	
Renal Allograft Rejection (Editorial), John P. Merrill.....(Dec)	56
Renal Failure, see <i>Acute</i> , and <i>Myelography</i>	
Renal Vascular Hypertension, see <i>Evaluation</i>	
[Report of Citizens Board of Inquiry into Health Services for Americans—A Dissenting Opinion], see <i>"Heal Yourself"</i>	

Report on Student Participation in Organized Medicine (Prepared by Medical Student Representatives to the CMA Committee on the Role of Medicine in Society) (Letter to Editor), William J. Nowack, Geoffrey A. Smith, Paul Barrett, Larry Freeman, and Peter Libby.....(Jul)	96
Research, Clinical, see <i>Phenylketonuria</i>	
Respiratory Diseases, see <i>Evaluation of the Role of Nitrogen Dioxide</i>	
Retrieval of Catheter Fragments—Report of Two Cases, Anthony M. Marlon, Lawrence H. Cohn, Thomas J. Fogarty and Donald C. Harrison (Nov)	61
Role of Medicine in Society Committee, CMA, see <i>Report on Student Participation</i>	
Rubella Vaccine Virus, see <i>Transmission of</i>	

S

[Sacramento County Medical Society], see <i>Certified Hospital Admission Program</i>	
Safe Approach to Carotid Endarterectomy, A, Louis L. Smith, Leland R. Raymond, Charles R. Simmons, and David B. Hinshaw.....(Dec)	4
San Diego County, University Hospital, and UC, San Diego, see <i>Specialty Conference</i>	
Secretion, Growth Hormone, see <i>Changing Concepts</i>	
Selective Service System and Physicians, (Information) L. S. Goerke.....(Aug)	97
Sensitivity Groups, see <i>Training Groups</i>	
Sex Education, see <i>Doctor</i>	
Smallpox Vaccination, see <i>Complication of SO₂</i> , see <i>Ox</i>	
Sodium Diatrizoate, see <i>Myelography</i>	
Soft [Plastic] Contact Lenses, Louis F. Saylor (Aug.)	96
Some Aspects of Medical Practice at UCLA, C. G. Craddock (Information).....(Sep)	89

Special Article:

Present and Future Role of Blue Shield, Carl E. Anderson.....(Sep)	74
Community College Health Services—A Health Care Crisis, E. D. Lovett.....(Nov)	66
Editorial, Henry B. Bruyn.....(Nov)	51
"Heal Yourself" [Dissenting Opinion of Report of Citizens Board of Inquiry into Health Services for Americans], Gerald Besson.....(Dec)	79

Specialty Conferences:

Syphilis (UC, Los Angeles, and Harbor General Hospital Teaching Conference in Infectious Diseases), Participants: James N. Miller, James R. Nelson, Ronald M. Reisner, and Jerrold A. Turner.....(Aug)	47
Tetanus (UC, San Diego, and University Hospital of San Diego County), Participants: William L. Nyhan, James D. Connor, Robert N. Hamburger, John H. Kerr, and Joc Young.....(Oct)	24
Editorial, John V. Bennett.....(Oct)	51
Nephrotic Syndrome (UC, San Francisco, Medical Grand Rounds), Participants: Laurence E. Earley, Richard J. Havel, James Hopper, Jr., and Henry Gausz.....(Nov)	23
Editorial, Arnold S. Relman.....(Dec)	58

Spectrum of Fungal Endocarditis, The (Medical Staff Conference).....(Oct)	34
Spherocytosis, see <i>Isotope Evaluation</i>	
Splenic Size, see <i>Isotope Evaluation</i>	

Statement Regarding Thioridazine [UC Fall Symposium on Obstetrics and Gynecology], Correction, see <i>Iatrogenic Embryonic Defects</i>	
[Statement] Selective Service System and Physicians, L. S. Goerke (Information)..... (Aug)	94
Stenosis, see <i>Tracheal</i>	
Stroke Patient, see <i>Orthopedic Rehabilitation</i>	
Synergistic Danger in Ketamine [Ketalar®, Ketaject®] and Innovar® (Letter to Editor), Edward R. Bloomquist (Nov)	64
Syphilis, see <i>Premarital Examinations</i>	
Syphilis, see <i>Venereal Disease</i>	
Syphilis (UC, Los Angeles, and Harbor General Hospital Teaching Conference in Infectious Diseases), Participants: James N. Miller, James R. Nelson, Ronald M. Reisner, and Jerrold A. Turner (Aug)	47
T	
Testing, Health, see <i>Multiphasic</i>	
Tetanus (UC, San Diego, and University Hospital of San Diego County), Participants: William L. Nyhan, James D. Connor, Robert N. Hamburger, John H. Kerr and Joe Young..... (Oct)	24
Editorial, John V. Bennett..... (Oct)	51
Tetanus—The Role of Diazepam in Therapy (Editorial), John V. Bennett..... (Oct)	51
[T-Groups], see <i>Training Groups</i>	
Therapeutic Abortions—A Review of 567 Cases, Paul H. Brenner, Edward J. Kirshen and Joseph M. Didio (Jul)	20
Therapeutic Abortions in California, E. W. Jackson, M. Tashiro and G. C. Cunningham..... (Jul)	28
Thioridazine, see <i>Iatrogenic Embryonic Defects</i>	
Thyroid Storm—A Review of Cases at University of California, San Francisco, Michael Roizen and Charles E. Becker..... (Oct)	5
Tracheal Stenosis, D. Frederick Knudsen and Roy Cohn (Sep)	1
Training Groups, Encounter Groups, Sensitivity Groups and Group Psychotherapy, Louis A. Gottschalk, E. Mansell Pattison and Donald W. Schafer (Aug)	87
Transmission of Rubella Vaccine Virus from Vaccines to Contacts, Jeanette Wilkins, John M. Leedom, Margaret A. Salvatore and Bernard Portnoy (Nov)	16
Transplanted Kidneys, see <i>Functional Aspects</i>	

Trauma, see <i>Blunt Laryngotracheal</i>	
Treatment, Psychiatric, see <i>New Methods of</i>	
Treatment with Human Growth Hormone (Li) for over 8 years—Effects of Long-Term Therapy in a Pituitary Dwarf, Roberto F. Escamilla and Peter H. Forsham (Dec)	72
Triamcinolone-Procaïne in the Treatment of Zoster and Postzoster Neuralgia, Ervin Epstein.. (Aug)	6
Tumor Registry, see <i>Cancer of the Pancreas</i>	

U

[UC Fall Symposium on Obstetrics and Gynecology—Correction], see <i>Iatrogenic Embryonic Defects</i>	
UC, LA Medical Practice, see <i>Some Aspects</i>	
UC, Los Angeles, see <i>Specialty Conferences</i>	
UC, San Diego, see <i>Specialty Conferences</i>	
UC, San Francisco, see <i>Specialty Conferences</i> , and <i>Medical Staff Conferences</i>	
UC, San Francisco, see <i>Thyroid Storm</i>	
Unified or Separate [CMA and AMA Membership], see <i>Question</i>	
United or Separate?..... (Aug)	77
University Hospital of San Diego County, and UC, San Diego, see <i>Specialty Conferences</i>	
Urban Growth, see <i>Air Pollution</i>	
Urinary Infections, see <i>Recurrent</i>	

V

Vaccine Virus, see <i>Transmission of Rubella</i>	
Venereal Disease, see <i>Progonasyl for</i>	
Venereal Disease Education (Letters to Editor), Mary Riggs..... (Oct)	74
Vaccination, Smallpox, see <i>Complication of</i>	
Venereal Disease Epidemic (Editorial), Walter H. Smartt (Aug)	78
Letter to Editor, Erwin H. Braff..... (Oct)	75
Voluntary vs. Compulsory, see <i>DOA</i>	

W

Water, see <i>Conserving</i>	
Watts Health Miracle, The (Letter to Editor), Elmer A. Anderson..... (Nov)	65

X

X-ray Operators Must Have Certification (Page End)..... (Oct)	81
---	----

Z

Zoster and Postzoster Neuralgia, see <i>Triamcinolone-Procaïne</i>	
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application for **HOTEL ACCOMMODATIONS**

ONE-HUNDRED-FIRST *Annual Session*

CALIFORNIA MEDICAL ASSOCIATION

And

First Invitational Western States

Scientific Assembly

FEBRUARY 12-16, 1972

SAN FRANCISCO HILTON HOTEL, SAN FRANCISCO

REGISTRATION OPENS IN MAIN LOBBY, FRIDAY AFTERNOON, FEBRUARY 11

SCIENTIFIC SESSIONS BEGIN SATURDAY MORNING, FEBRUARY 12

HOUSE OF DELEGATES OPENING SESSION SATURDAY AFTERNOON, FEBRUARY 12

1. Fill in the form below *completely* for room accommodations at the CMA's 1972 Annual Session.
2. Your reservation request should include the definite date and hour of your arrival and departure.
3. All reservations, *except for suites*, must be made through the San Francisco Hilton Hotel, Mason at O'Farrell Street, San Francisco, Ca. 94102, by January 12, 1972.
4. **ALL SUITE RESERVATIONS MUST BE CLEARED THROUGH THE CMA CONVENTION OFFICE, SAN FRANCISCO. IF YOU ARE REQUESTING A SUITE, DIRECT YOUR REQUESTS TO: CMA CONVENTION OFFICE, 693 SUTTER STREET, SAN FRANCISCO, CA. 94102.**
5. **CANCELLATIONS:** Please notify San Francisco Hilton Hotel, Mason at O'Farrell Street, San Francisco, Ca. 94102, of all cancellations.
CHANGES: All other changes are also to be made directly with hotel at all times.

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Singles	\$22-38	\$37-43
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2 Bedroom suites	\$97 & up	\$147 & up

SEND TO: SAN FRANCISCO HILTON HOTEL RESERVATIONS

Mason at O'Farrell Streets, San Francisco, Ca. 94102

Please reserve the following accommodations for the CMA's 1972 Annual Session in San Francisco, February 12-16, 1972:

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THE NAME AND ADDRESS OF EACH HOTEL GUEST MUST BE LISTED. Include names and addresses of *each* person in a double or twin-bedded room, and names and addresses of *all other persons* for whom you are requesting reservations.

Your Name: Officer?..... Delegate? Alternate?..... Speaker?

Address: County

City and State Zip Code

GUESTS' NAMES AND ADDRESSES:

.....
.....
.....

101st Annual Session Program

and First Western States Invitational Scientific Assembly

Hilton Hotel

Mason and O'Farrell • San Francisco

February 12 to 16, 1972



- *Scientific Section Programs*
- *Three General Meetings*
- *Special Conferences*
- *Scientific and Technical Exhibits*
- *Meetings of the House of Delegates*

California Medical Association

CALIFORNIA MEDICAL ASSOCIATION 101st ANNUAL SCIENTIFIC ASSEMBLY
February 12-16, 1972 - Hilton Hotel, San Francisco
DAILY SCHEDULE

SATURDAY, FEBRUARY 12		Room	Morning	Afternoon	All Day
Section Meetings:					
Allergy		Continental Parlors #8 and #9			9:00
Orthopedics		Continental Parlor #3	9:00		
Pathology		Continental Parlor #7	9:00		
Physical Medicine and Rehabilitation		Walnut		2:00	
Special Conferences:					
American College of Chest Physicians		Continental Parlors #1 and #2			9:00
Symposium on Extramarital Pregnancy		Continental Ballroom #5	9:00		
Pelvic Cancer in the Liberated Sex		Continental Ballroom #4		2:00	
General Meeting:					
Interdisciplinary Approaches for High Quality Health Care		Continental Ballroom #6		2:00	
CMA HOUSE OF DELEGATES—Opening Session					
Scientific and Organizational Exhibits		Imperial Ballroom		2:00	
		California and Tower Lobby			9:00
SUNDAY, FEBRUARY 13					
Section Meetings:					
Dermatology		Continental Parlor #7	8:30		
General and Family Practice		Continental Parlor #3	9:00		
Internal Medicine/Radiology/Chest Physicians		Continental Ballroom #5	9:30		
Ophthalmology		Continental Parlors #8 and #9			9:30
Otolaryngology/Neurology		Walnut	9:00		
Otolaryngology/Plastic Surgery		Teakwood		2:00	
Plastic Surgery		Teakwood			9:00
Psychiatry/Neurology		Toyon			9:00
Radiology/Internal Medicine/Chest Physicians		Continental Ballroom #5	9:30		
Special Conferences:					
Physician Responsibility and Drug Abuse		Continental Ballroom #4			9:00
Pathology Conference		Continental Parlors #1 and #2			9:00
General Meeting:					
Computer Applications Toward Delivery of High Quality Health Care		Continental Ballroom #6		2:00	
Scientific and Organizational Exhibits		California and Tower Lobby			9:00

MONDAY, FEBRUARY 14				
Section Meetings:	Room	Morning	Afternoon	All Day
Anesthesiology	Continental Parlor #7			9:00
Anesthesiology/Obstetrics and Gynecology	Continental Parlor #7		2:00	
General Surgery	Continental Parlor #8		12:00	
Internal Medicine	Whitney/Shasta/Tamalpais	9:00		
Obstetrics and Gynecology	Continental Parlor #9	9:00		
Obstetrics and Gynecology/Anesthesiology	Continental Parlor #7		2:00	
Preventive Medicine and Public Health (see Venereal Disease Symposium below)	Continental Ballroom #5			9:00
Special Conferences:				
Symposium on Venereal Disease (Sections on Preventive Medicine and Public Health, Dermatology, Obstetrics/ Gynecology, and Urology)	Continental Ballroom #5			9:00
The Health Care Assistant	Continental Ballroom #6	9:00		
Pollution Problems Have Many Facets	Continental Parlor #3	9:00		
General Meeting:				
Consumer Education and Participation for High Quality Health Care	Continental Ballroom #6		2:00	
Scientific and Organizational Exhibits	California and Tower Lobby			9:00
TUESDAY, FEBRUARY 15				
Section Meetings:				
Industrial Medicine and Surgery	Continental Parlor #3	9:00		
Pediatrics	Rosewood			9:30
Urology	Walnut			9:00
Special Conferences:				
Medical Education Today—for What?	Continental Parlors 7, 8, and 9	9:00		
Emergency and Disaster Preparedness	Continental Ballroom #6			9:00
CMA HOUSE OF DELEGATES	Imperial Ballroom		1:00	
Scientific and Organizational Activities	* California and Tower Lobby			9:00
WEDNESDAY, FEBRUARY 16				
CMA HOUSE OF DELEGATES	Imperial Ballroom	9:00 to conclusion of business		

TABLE OF CONTENTS

Daily Schedule	2	General and Family Practice	20
Information	6	General Surgery	20
Guest Speakers	7	Industrial Medicine and Surgery	21
Participants	9	Internal Medicine	21
Announcement, CMA Certification Program	12	Obstetrics and Gynecology	22
Special Conferences		Ophthalmology	22
Sixth Annual Cancer Symposium	13	Orthopedics	23
Symposium on Extramarital Pregnancy	13	Otolaryngology	23
American College of Chest Physicians	13	Pathology	23
Physician Responsibility and Drug Abuse	14	Pediatrics	24
Pathology Conference	15	Physical Medicine and Rehabilitation	24
Symposium on Venereal Disease	15	Plastic Surgery	24
Pollution Problems Have Many Facets	16	Preventive Medicine and Public Health	25
The Health Care Assistant in California	16	Psychiatry and Neurology	25
Medical Education Today—for What?	16	Radiology	26
Emergency and Disaster Preparedness	16	Urology	26
General Meetings	18	Woman's Auxiliary	27
Scientific Section Meetings		House of Delegates Agenda	28
Allergy	19	Proposed Constitutional Amendment	30
Anesthesiology	19	Financial Report	31
Dermatology	20		

ACKNOWLEDGEMENT

During 1972 the twentieth Advisory Panel will come into being in the unique Scientific Board structure of the California Medical Association. Each medical specialty section is strengthened by such a panel, with representation from the specialty societies and from the medical school departments. The contribution these blue-ribbon panels have already made in helping to improve the educational quality of the Annual Scientific Assembly is significant. Each 16-man panel includes the leadership in a specialty. In the aggregate we are fortunate to have the assistance and cooperation of some three hundred of the best minds in California to help us plan this assembly, and to work with us in a continuing effort to improve its educational work.

The 101st Annual Session is subtitled "First Western States Invitational." We believe the participation of physicians from other western states, which has long been a feature of the assembly, should be recognized and will increase as the educational stature of the assembly continues to grow. Certainly the efforts at CMA in the voluntary certification of physicians and accreditation of continuing medical education activities have received wide interest, and must be accompanied by appropriate efforts to improve major medical meetings such as the Annual Scientific Assembly. This year many of the sessions are combined, co-sponsored and interdisciplinary. This reflects, in part, the unifying influence of the Scientific Board's program to bring together the many mansions of medicine.

JOHN B. DILLON, M.D., *Chairman*
Committee on Scientific Assemblies
of the Scientific Board

California Medical Association



ROBERTA F. FENLON, *President*



JEAN F. CRUM, *President-Elect*

Information

BADGES:

It is important that badges be worn at all times. Admission to scientific meetings is by badge only.

COUNCIL:

The Council will meet Friday, February 11, 3:00 p.m., and Saturday, February 12, 9:00 a.m. to noon. Rooms will be posted on the hotel schedule boards.

HOUSE OF DELEGATES:

For meeting times, places, and agenda—see pages 28-31. The list of delegates and alternates will appear in the January issue of *CALIFORNIA MEDICINE*.

EMERGENCY CALLS AND MESSAGES:

Convention Emergency Call Number—(415) 776-1390. From 8:30 a.m. to 5:00 p.m., Saturday, February 12 through Wednesday, February 16.

MESSAGE CENTER:

Provided through the courtesy of the Pacific Telephone Company—(415) 776-1390.

Location: East Lounge, San Francisco Hilton Hotel.
Hours: 8:30 a.m. to 5:00 p.m.

The Association will *attempt* to transmit *emergency* messages to the individual physician. Each physician should notify his own office of the exact times and meetings he plans to attend, and the Convention number.

Routine Messages: Will be kept at the Message Center in the East Lounge.

Physicians are requested to check with the Message Center at least once a day.

INDEX TO PARTICIPANTS:

See pages 9-11.

TECHNICAL EXHIBITS:

Hilton Plaza and the Franciscan Room.

SCIENTIFIC AND ORGANIZATIONAL EXHIBITS:

Tower Room, California Room, and North Lounge.

REGISTRATION AND INFORMATION:

Registration and information desks are located at the *Main Entrance to the Hilton Plaza*. All members, guests and visitors are requested to register immediately on arrival. There is no charge for registration.

Desks are open Friday after 1:00 through Wednesday.

Admission to the general and section meetings and exhibit areas is by badge only.

Members wishing to vote in specialty sections must indicate appropriate section when registering; voting in other sections will not be allowed.

QUALIFICATIONS/REQUIREMENTS FOR REGISTRATION:

All M.D.s with credentials showing that they hold valid license to practice medicine. (Membership card: CMA; county medical society/association; AMA.)

Medical students upon presentation of credentials from their medical schools. (Membership card, Student Medical Association, or letter from Dean's office.)

Medical Assistants upon presentation of a letter from the physician-employer or C.M.A.A. membership card.

Military paramedical personnel upon presentation of a letter requesting their admittance, written by their commanding officer.

Dentists (D.D.S.)—Doctors of Veterinary medicine (D.V.M.)—registered nurses (R.N.)—student nurses—x-ray technicians—laboratory technicians—allied public health personnel—and others will be admitted provided they have proper identification.

ALL QUESTIONS ON ADMISSION will be passed upon by a member of the Committee on Registration present at the desk.

Guest Speakers

GENERAL MEETINGS

Saturday, February 12 2:00 p.m.—Continental Ballroom #6

Interdisciplinary Approaches for High Quality Health Care

- Stephen Morris, President, American Hospital Association, Phoenix
- Fred I. Gilbert, Jr., M.D., Medical Director, Medical Research Institute, Honolulu

Sunday, February 13 2:00 p.m.—Continental Ballroom #6

Computer Applications Toward Delivery of High Quality Health Care

- Donald A. B. Lindberg, M.D., Chairman of Computer and Information Sciences, Director of Clinical Information Systems, University of Missouri, Columbia
- Steven R. Yarnell, M.D., Assistant Professor, Department of Medicine, University of Washington School of Medicine; Associate Director, Washington/Alaska Regional Medical Programs, Seattle

Monday, February 14 2:00 p.m.—Continental Ballroom #6

Consumer Education and Participation for High Quality Health Care

- Mrs. Eleanor A. Brand, President, Board of Directors, The Group Health Cooperative of Puget Sound, Seattle

Out-of-State Guests

SECTIONS and SPECIAL CONFERENCES

• Allergy

Elliott Middleton, Jr., M.D., Director, Clinical Services and Research, Childrens Asthma Research Institute and Hospital, Denver

Roy Patterson, M.D., Ernest S. Bazley Professor, Allergy and Immunology, Northwestern University Medical School, Chicago

• General and Family Practice

Ralph A. Shaw, M.D., Ph.D., Director of Clinical Chemistry, Department of Laboratory Medicine, Hahneman Medical College and Hospital, Philadelphia

• General Surgery

Bentley P. Colcock, M.D., Associate Clinical Professor of Surgery, Boston University School of Medicine, Boston

• Industrial Medicine and Surgery

Charles C. Gullett, M.D., Medical Director, Trans World Airlines, Kansas City, Missouri

George J. Kidera, M.D., Medical Director, United Air Lines, Chicago

Ludwig G. Lederer, M.D., Ph.D., Medical Director, American Airlines, New York City

• Internal Medicine, Radiology, Chest Physicians

Robert Fraser, M.D., McGill University Faculty of Medicine, Montreal

E. G. Marshall, "Chief of Staff, David Craig, M.D.," in the medical segment of "The Bold Ones," NBC TV, Mount Kisco, New York

• Obstetrics and Gynecology

T. N. Evans, M.D., Acting Dean; Professor and Chairman, Department of Gynecology and Obstetrics, Wayne State University School of Medicine, Detroit

• Ophthalmology

Arthur H. Keeney, M.D., Professor and Chairman, Department of Ophthalmology, Temple University of the Commonwealth System of Higher Education School of Medicine, Philadelphia

• Pediatrics

C. Henry Kempe, M.D., Professor and Chairman, Department of Pediatrics, University of Colorado Medical Center, Denver

Harry Meyer, M.D., Chief, Division of Biostandards, National Institutes of Health, Bethesda, Maryland

Emerson C. Walden, M.D., President, National Medical Association, Baltimore

• Physical Medicine and Rehabilitation

John S. Young, M.D., Director, Spinal Injury Service, Good Samaritan, Phoenix

• Sixth Annual Cancer Symposium

John L. Lewis, Jr., M.D., Chief, Gynecology Service, Memorial Hospital for Cancer and Allied Diseases, New York City

Felix Rutledge, M.D., Gynecologist-in-Chief, University of Texas M.D. Anderson Hospital and Tumor Institute at Houston

Howard Ulfelder, M.D., Chief, Gynecology Service, Massachusetts General Hospital, Boston

• Disaster and Emergency Medical Care

Doctor Georges P. Bergot, Medical Director, Orly Airport, Paris

Harold Gibbons, M.D., Public Health Department, Salt Lake City, Utah

• Physician Responsibility and Drug Abuse

Stanley Einstein, Ph.D., Professor and Director, Division of Drug Abuse Martland Hospital Unit, New Jersey College of Medicine and Dentistry, Newark

• Occupational Health

Marcus M. Key, M.D., Director, National Institute of Occupational Safety and Health, Rockville, Maryland

INDEX TO PARTICIPANTS

PARTICIPANTS FROM OUT-OF-STATE

ergot, Georges P., Paris, France.....	17	Cady, Lee D., Jr., Los Angeles.....	18
rand, Mrs. Eleanor A., Seattle.....	18	Caplan, Harvey W., Oakland.....	13
olecock, Bentley P., Boston.....	20	Carr, Ian R., San Francisco.....	14
instein, Stanley, Newark, New Jersey.....	14	Chandor, Stebbins B., Los Angeles.....	23
vans, T. N., Detroit.....	22	Chesbro, Wayne P., Berkeley.....	17, 21
raser, Robert, Montreal.....	21, 26	Chen, Donald H., South San Francisco.....	17
ibbons, Harold, Salt Lake City.....	17	Clark, Daniel W., San Jose.....	16
ilbert, Fred I., Jr., Honolulu.....	18	Clark, Miss Mary Lou, San Francisco.....	26
ullett, Charles C., Kansas City, Missouri.....	21	Cohen, David D., Los Angeles.....	19
eeney, Arthur H., Philadelphia.....	22	Cohn, Keith E., San Francisco.....	14
empe, C. Henry, Denver.....	24	Colcock, Bentley P., Boston.....	20
ey, Marcus M., Rockville, Maryland.....	16	Collins, Robert C., San Francisco.....	21
idera, George J., Chicago.....	21	Comarr, A. Estin, Long Beach.....	24
ederer, Ludwig G., New York City.....	21	Conaty, Joseph Pierce, Fullerton.....	23
ewis, John L., Jr., New York City.....	13	Corday, Eliot, Beverly Hills.....	14
indberg, Donald A. B., Columbia, Missouri.....	18	Cowan, Michael N., San Mateo.....	17
arshall, E. G., Mount Kisco, New York.....	21, 26	Crum, Jean F., Downey.....	18
eyer, Harry, Bethesda, Maryland.....	24	Cutting, Cecil C., Oakland.....	18
iddleton, Elliott, Jr., Denver.....	19		
orris, Stephen, Phoenix.....	18	Davis, Edward H., Beverly Hills.....	26
atterson, Roy, Chicago.....	19	Davis, H. Glenn, Sacramento.....	22
utledge, Felix, Houston.....	13	Demorest, Byron H., Sacramento.....	23
aw, Ralph A., Philadelphia.....	20	Dresner, Ellis, Los Angeles.....	23
lfelder, Howard, Boston.....	13	Drutz, David J., San Francisco.....	15, 25
alden, Emerson C., Baltimore.....	24	Duhl, Leonard J., Berkeley.....	18
arnell, Steven R., Seattle.....	18	Dunphy, J. Englebert, San Francisco.....	20
oung, John S., Phoenix.....	24		
		Edgington, Thomas S., La Jolla.....	23
dams, Robert M., Palo Alto.....	20	Edmunds, L. Henry, San Francisco.....	13
dmirand, William, San Francisco.....	22	Einstein, Hans E., Bakersfield.....	14
dour, Kedar, Oakland.....	23	Einstein, Stanley, Newark, New Jersey.....	14
lderman, Edwin, Palo Alto.....	14	Elmendorf, Thomas N., Willows.....	17
lmond, Bayard W., Jr., San Francisco.....	22	Eltringham, James R., Stanford.....	13
cher, Loran, Sacramento.....	15	Epstein, Leon, San Francisco.....	26
rmstrong, William T., San Francisco.....	14	Evans, T. N., Detroit.....	22
shley, Franklin L., Los Angeles.....	24		
yres, William H., San Mateo.....	25	Falees, Edward, San Francisco.....	24
		Fallat, Robert, San Francisco.....	13
aker, Cleve B., Woodland.....	15, 25	Farber, Eugene M., Palo Alto.....	20
allard, Charles A. C., Los Angeles.....	19, 22	Feigen, Gerald M., San Francisco.....	15, 25
amman, Henry, Sacramento.....	22	Fink, Aaron J., Mountain View.....	15, 25
ard, Gregory, San Francisco.....	24	Fishman, Noel H., San Francisco.....	13
arsky, Morley, San Diego.....	23, 25	Fraser, Robert, Montreal.....	21
atzle, J. Harold, Riverside.....	24	Freedman, Robert I., Downey.....	20
ecker, Charles E., San Francisco.....	22	Fudenberg, H. Hugh, San Francisco.....	23
enioff, Mortimer A., San Francisco.....	13		
ennington, James L., San Francisco.....	15	Galant, Stanley P., Irvine.....	19
ergot, Georges P., Paris, France.....	17	Gamble, Stephen W., Los Angeles.....	16
lessum, William T., Irvine.....	18	Gerbode, Frank, San Francisco.....	14
lodget, Rush M., Jr., Redding.....	22	Gibbons, Harold, Salt Lake City.....	17
loomquist, Edward R., Glendale.....	14	Gilbert, Fred I., Honolulu.....	18
oyle, William F., San Francisco.....	23	Cofman, Helen, San Francisco.....	23
rand, Mrs. Eleanor A., Seattle.....	18	Goldman, Leon, San Francisco.....	21
rewin, Austin, San Francisco.....	22	Goldsmith, John R., Berkeley.....	19
ridge, Robert A. C., San Diego.....	26	Goldsmith, Sadja, San Francisco.....	24
rotman, Martin, San Francisco.....	22	Goldstein, Elliot, Davis.....	22
runstetter, Richard W., San Francisco.....	25	Gonda, Thomas A., Stanford.....	18
umcke, Harry J., Jr., San Mateo.....	23, 25	Goode, Richard L., Stanford.....	23, 25
urch, Buford H., Martinez.....	13	Gordon, Jack T., San Francisco.....	15
urnside, Mrs. Irene, Lafayette.....	26	Gorney, Mark, San Francisco.....	24
		Graff, Norman I., San Mateo.....	26
		Graves, William K., San Francisco.....	22
		Greenspan, Richard, San Francisco.....	21, 26
		Griffeath, Harold I., San Francisco.....	14
		Grollman, Julius H., Jr., Los Angeles.....	21, 26

Gullett, Charles C., Kansas City.....	21
Hall, Albert D., San Francisco.....	20
Haller, Yoel I., San Francisco.....	15, 25
Hanson, Frederick W., Davis.....	22
Hardy, Kenneth L., Oakland.....	13
Harp, Vernon C., Jr., San Francisco.....	14
Harwell, Julian L., Pasadena.....	19
Hays, Marvin B., Eureka.....	17
Henkin, Melvyn L., Encino.....	19, 22
Hill, J. Donald, San Francisco.....	13
Hine, Charles C., Piedmont.....	16
Hinman, Frank, Jr., San Francisco.....	26
Hoffman, Julien I. E., San Francisco.....	14
Hull, Osman H., Monterey.....	23
Irwin, Donald, Sacramento.....	16
Jacobs, Alvin H., San Francisco.....	24
Jacobs, Paul H., Palo Alto.....	20
Jampolsky, Gerald G., Tiburon.....	23
Jenkins, William M., Oakland.....	24
Judkins, Melvin P., Loma Linda.....	20, 21, 26
Jutzy, Roy, Loma Linda.....	21, 26
Kalmansohn, Robert B., Los Angeles.....	21, 26
Kaltreider, H. Benfer, San Francisco.....	13
Kambara, George K., Los Angeles.....	22
Kaplan, Ernest N., Stanford.....	24
Kauffman, Raymond R., San Mateo.....	23, 25
Kaufman, Herbert S., San Francisco.....	13
Keeney, Arthur H., Philadelphia.....	23
Keller, David W., Palo Alto.....	22
Kempe, C. Henry, Denver.....	24
Kempson, Richard L., Stanford.....	13
Kerth, William J., San Francisco.....	21, 26
Ketterer, Warren A., Berkeley.....	15, 24, 25
Key, Marcus M., Rockville, Maryland.....	16
Khoury, Nicholas, Los Angeles.....	15
Kidera, George J., Chicago.....	21
Kirtland, Howard B., San Diego.....	16
Korn, David, Stanford.....	23
Krotcher, Lester C., San Francisco.....	20
Kumagai, Lindy F., Davis.....	21
Lamson, Baldwin G., Los Angeles.....	18
Laskow, Leonard, San Francisco.....	13
Laub, Donald R., Stanford.....	24
Laursen, Elmer, San Francisco.....	13
Lebherz, Thomas, Los Angeles.....	22
Lederer, Ludwig G., New York City.....	21
Leeds, Sanford E., San Francisco.....	13
Lennette, Edwin H., Berkeley.....	24
Levy, Leonard A., San Francisco.....	20
Lewis, John L., Jr., New York City.....	13
Lieberman, Jack, Duarte.....	19
Lindberg, Donald A. B., Columbia, Missouri.....	18
Lipscomb, Paul R., Davis.....	23
Lipson, Leon W., Palo Alto.....	19
Lukes, Robert, Los Angeles.....	23
Lyons, Thomas W., La Mesa.....	17
Maloney, James V., Jr., Los Angeles.....	21, 26
Marshall, E. G., Mount Kisco, New York.....	21, 26
May, Angelo M., San Francisco.....	21, 26
May, Ivan, Oakland.....	13
Meine, Emile L., Jr., Panorama City.....	17
Merkel, Charles G., San Francisco.....	16
Meyer, Harry, Bethesda, Maryland.....	24
Middleton, Elliott, Jr., Denver.....	19

Milby, Thomas H., Berkeley.....	16
Miller, Ronald D., San Francisco.....	19
Milligan, Richard S., Modesto.....	17
Millman, Milton, San Diego.....	19
Mitchell, Ellis N., Greenbrae.....	15, 25
Monsen, David C. G., Los Angeles.....	18
Morris, Stephen, Phoenix.....	18
Morris, William J., San Francisco.....	24
Murphy, Stephen P., San Diego.....	17
McDonald, John S., Los Angeles.....	22
McDowell, Milton K., Kentfield.....	19
McGann, Benson R., Los Altos.....	20
McGarvey, William M., San Francisco.....	23, 25
McHenry, Malcolm M., Sacramento.....	14
McKee, William D., Palo Alto.....	19
McLarty, William, Berkeley.....	16
McLin, Patrick H., San Rafael.....	26
Neilsen, Ivan R., Loma Linda.....	18
Nelson, Donald, Redding.....	17
Newland, John E., Santa Ana.....	19
Niemeyer, Arnold C., Palos Verdes Estates.....	16
Norling, Lowell, East Palo Alto.....	18
Novey, Harold S., Whittier.....	19
Ockner, Robert K., San Francisco.....	22
Opfell, Richard, Santa Ana.....	18
Orloff, Marshall J., San Diego.....	20
Patterson, Roy, Chicago.....	19
Peskin, Gerald W., San Diego.....	20
Petoyan, Arthur S., Granada Hills.....	19, 22
Pheasant, Homer C., Los Angeles.....	18
Phillips, Theodore L., San Francisco.....	21, 26
Pinto, Douglas W., San Francisco.....	20
Popper, Robert W., San Francisco.....	14
Pulec, Jack L., Los Angeles.....	23
Quickert, Marvin H., San Jose.....	23, 25
Quinn, William F., Los Angeles.....	14
Ramseyer, J. Carroll, Los Angeles.....	23, 26
Redeker, Allen G., Los Angeles.....	23
Richards, Victor, San Francisco.....	13
Rickett, Mrs. Mabel S., Berkeley.....	15, 25
Riggall, Evison R. (Ronald), Oakland.....	13
Robinson, Saul, San Francisco.....	14
Robinson, Tom W., Newport Beach.....	15, 25
Russell, Warren M., San Francisco.....	21, 26
Rutledge, Felix, Houston.....	13
Saenz, Lionel, San Francisco.....	23
Salmon, Sydney E., San Francisco.....	13
Samilson, Robert L., San Francisco.....	23
Samson, Paul C., Oakland.....	13
Sayer, William J., Palo Alto.....	19
Scheinman, Melvin M., San Francisco.....	14
Schwartz, Francis R., San Francisco.....	21
Schweitzer, Robert J., Oakland.....	13
Selzer, Arthur, San Francisco.....	14
Sharrocks, Horace F., Sebastopol.....	15
Shav, Ralph A., Philadelphia.....	20
Shinefield, Henry R., San Francisco.....	24
Shlens, Robert D., Los Angeles.....	25
Skinner, Donald G., Los Angeles.....	26
Smart, William R., San Rafael.....	20
Smartt, Walter H., Los Angeles.....	16, 25
Smith, David E., San Francisco.....	14
Sokoloff, Tilden H., San Francisco.....	20
Solis, Miss Faustina, La Jolla.....	18

tamey, Thomas A., Stanford.....	26
teinbach, Howard L., San Francisco.....	21, 26
teinman, Paul A., Greenbrae.....	19
tern, Earl L., San Francisco.....	22
umner, Austin J., San Francisco.....	23
vihus, Richard H., Santa Cruz.....	15
abershaw, Irving R., Berkeley.....	16
anagho, Emil A., San Francisco.....	26
aylor, Robert G., Sacramento.....	24
ucker, Harvey, San Francisco.....	13
uffanelli, Denny L., San Francisco.....	15, 25
lfelder, Howard, Boston.....	13
izzard, Joseph N., Los Gatos.....	24
valden, Emerson C., Baltimore.....	24
valton, Charles O., Menlo Park.....	25
valton, Robert G., Modesto.....	24
varner, Nancy, Los Angeles.....	15

Wangh, Theodore R., Orange.....	23
Way, Lawrence W., San Francisco.....	20
Weinstein, Harry, San Francisco.....	26
Weissman, Irving, Stanford.....	23
Welch, Richard B., San Francisco.....	23
Wilde, N. John, Fresno.....	23, 25
Wilhelm, Anthony J., Berkeley.....	13
Williams, Hibbard E., San Francisco.....	26
Wilson, Archie F., Irvine.....	19
Winton, Keith, Livingston.....	18
Wolf, C. Richard, Berkeley.....	16
Wolfman, Earl F., Jr., Davis.....	20
Wood, Ronald M., Berkeley.....	15, 25
Wright, Robert, San Francisco.....	13
Wyman, Milford G., San Pedro.....	14
Yarnell, Steven R., Seattle.....	18
Yoder, Richard D., La Jolla.....	18
Young, John S., Phoenix.....	24
Zimmerman, Herbert H., Jr., Burlingame.....	16, 17

To Register — You MUST have proper identification

QUALIFICATIONS/REQUIREMENTS FOR REGISTRATION:

All M.D.s with credentials showing that they hold valid license to practice medicine. (Membership card; CMA; county medical society/association; AMA.)

Medical students upon presentation of credentials from their medical schools. (Membership card, Student Medical Association, or letter from Dean's office.)

Medical Assistants upon presentation of a letter from the physician-employer or C.M.A.A. membership card.

Military paramedical personnel upon presentation of a letter requesting their admittance, written by their commanding officer.

Dentists (D.D.S.)—Doctors of Veterinary medicine (D.V.M.)—registered nurses (R.N.)—student nurses—x-ray technicians—laboratory technicians—allied public health personnel—and others will be admitted provided they have proper identification.

ALL QUESTIONS ON ADMISSION will be passed upon by a member of the Committee on Registration present at the desk.

You may be reached through (415) 776-1390

EMERGENCY CALLS AND MESSAGES:

Convention Emergency Call Number—(415) 776-1390.

From 8:30 a.m. to 5:00 p.m., Saturday, February 12 through Wednesday, February 16.

MESSAGE CENTER:

Provided through the courtesy of the Pacific Telephone Company—(415) 776-1390.

Location: East Lounge, San Francisco Hilton Hotel.

The Association will *attempt* to transmit *emergency* messages to the individual physician. Each physician should notify his own office of the exact times and meetings he plans to attend, and the Convention number.

Routine Messages: Will be kept at the Message Center in East Lounge, San Francisco Hilton Hotel.

Physicians are *requested* to *check with the Message Center at least once a day.*

California Medical Association

CERTIFICATE

IN

CONTINUING MEDICAL EDUCATION

SPECIAL ANNOUNCEMENT

Each scientific program acceptable for Group A credit is so designated:

**Acceptable for Group A Credit under
the CMA Certification Program**

The majority of the other educational and scientific
programs are acceptable for Group B credit.

PHYSICIANS SHOULD REPORT
THE ACTUAL NUMBER OF
PROGRAM HOURS ATTENDED

Special Conferences

SATURDAY, FEBRUARY 12

Continental Ballroom #4

SIXTH ANNUAL CANCER SYMPOSIUM

*Sponsored jointly by the CMA Committee on Cancer;
the California Division and the Alameda, Contra
Costa, Marin, San Francisco, San Mateo,
and Santa Clara Units of the
American Cancer Society*

Pelvic Cancer in the Liberated Sex

Chairman: Victor Richards, M.D., San Francisco

Moderator: Robert J. Schweitzer, M.D., Oakland

2:00—Welcome: Victor Richards, M.D., San Francisco

2:05—Pathology of Pelvic Tumors—Richard L. Kempson, M.D., Stanford, by invitation

2:25—Early Diagnosis and Staging—John L. Lewis, Jr., M.D., New York City, by invitation

2:45—Surgery—Howard Ulfelder, M.D., Boston, by invitation

3:05—Radiation Therapy—James R. Eltringham, M.D., Stanford, by invitation

3:25—Endocrine Therapy and Chemotherapy—Sydney E. Salmon, M.D., San Francisco

3:45—Ovarian Cancer—Felix Rutledge, M.D., Houston, by invitation

4:05—PANEL DISCUSSION

Acceptable for Group A Credit under
the CMA Certification Program

SATURDAY, FEBRUARY 12

Continental Ballroom #5

Symposium on Extramarital Pregnancy

CMA Committee on Medicine and Religion

The role of the physician and the clergyman in counseling.
What should the unwed pregnant girl be advised to do—

get married?

put the baby out for adoption?

keep the baby, even though unwed?

have an abortion?

9:00—Harvey Caplan, M.D., Oakland, by invitation

9:15—Leonard Laskow, M.D., San Francisco

9:30—Reverend Elmer Laursen, San Francisco, by invitation

9:45—Reverend Anthony J. Wilhelm, Berkeley, by invitation

10:00—Recess

10:15—PANEL DISCUSSION

Response to questions from the audience

SATURDAY, FEBRUARY 12

Continental Parlors #1 and #2

AMERICAN COLLEGE OF CHEST PHYSICIANS

CALIFORNIA CHAPTER

Annual Meeting

*Two scientific sessions will take place
simultaneously in adjoining meeting rooms*

9:00—Continental Parlor #1

Chairman: Evison R. (Ronald) Riggall, M.D., Oakland
Co-Chairman: Mortimer A. Benioff, M.D., San Francisco

Introduction: Mortimer A. Benioff, M.D., San Francisco

9:05—Respiratory Diseases Due to Immune Deficiency States—
Herbert S. Kaufman, M.D., San Francisco

10:00—Aspects of Constant Positive Pressure Ventilation—
Harvey Tucker, M.D., San Francisco, by invitation

10:25—Recess

10:40—Continuous Monitoring of Respiratory Mechanics—
Robert Fallat, M.D., San Francisco

11:10—New Concepts of Wegeners Granulomatosis—Robert
Wright, M.D., San Francisco, by invitation

11:40—Pulmonary Hypersensitivity Reactions—H. Benfer Kal-
treider, M.D., San Francisco, by invitation

9:00—Continental Parlor #2

Chairman: Kenneth L. Hardy, M.D., Oakland

Introduction by the Chairman

9:05—Clinical Experience with Mediastinoscopy—Noel H.
Fishman, M.D., San Francisco

9:20—Lung Abscess Secondary to Pulmonary Infarction—Ivan
May, M.D., Oakland; Paul C. Samson, M.D., Oakland

9:35—Questions and Answers Session

9:45—Present-day Indications for Segmental Resection—Buford
H. Burch, M.D., Martinez, by invitation

10:00—Lymphatics of the Heart—Sanford E. Leeds, M.D., San
Francisco

10:15—Recess

10:30—Clinical Experience with Extra Corporeal Support for
Respiratory Insufficiency—J. Donald Hill, M.D., San
Francisco

10:45—Questions and Answers Session

11:00—Current Status of Lung Transplantation—L. Henry Ed-
munds, M.D., San Francisco, by invitation

Luncheon

American College of Chest Physicians,
California Chapter

Business Meeting and Election of Officers

Presentation of "Man-of-the-Year" Award

Gordon Diddy Memorial Lecture: *Coccidioidomycosis*—
Hans E. Einstein, M.D., Bakersfield

Tickets must be purchased in advance.
Send checks (in the amount of \$6.00) to:

Robert Stone, M.D., President
ACCP, California Division
2930 Summit Street
Oakland, California 94609

2:00—

Continental Parlor #1

Chairman: Vernon C. Harp, Jr., M.D., San Francisco
Introduction by the Chairman

2:05—Analysis of Ventricular Function Utilizing Digital Computer Techniques—Edwin Alderman, M.D., Palo Alto, by invitation

2:20—Isotope Scan of the Acutely Infarcted Heart—Eliot Corday, M.D., Beverly Hills

2:35—Personal Heart Rate Monitor in Therapeutic Exercise—Harold I. Griffeath, M.D., San Francisco

2:50—The Coronary Athlete—William T. Armstrong, M.D., San Francisco

3:05—Indications for Coronary Angiography and Venous Bypass Graft—Arthur Selzer, M.D., San Francisco

3:20—Questions and Answers Session

3:35—Recess

3:50—Mechanisms and Diagnosis of Ventricular Arrhythmias—Milford G. Wyman, M.D., San Pedro

4:05—Therapy of Arrhythmias in the Ambulatory Patient—Keith E. Cohn, M.D., San Francisco

4:20—Clinical Applications of His Bundle Recordings—Melvin M. Scheinman, M.D., San Francisco, by invitation

4:35—Treadmill Performance After Myocardial Infarction: A Comparison of Exercise Retaining and Surgical Bypass—Malcolm M. McHenry, M.D., Sacramento

2:00—

Continental Parlor #2

Chairman: Frank Gerbode, M.D., San Francisco

2:00—The Diagnostic Challenge of Congenital Heart Disease in the Sick Infant—Ian R. Carr, M.D., San Francisco

2:20—Spontaneous Closure of Ventricular Septal Defects—Julien I. E. Hoffman, M.D., San Francisco, by invitation

2:40—Congenital Abnormalities of the Coronary Arteries—Robert W. Popper, M.D., San Francisco

3:00—Catheter Therapy of Congenital Heart Disease—Ian C. Carr, M.D., San Francisco

3:30—Surgical Correction of Congenital Heart Disease—Frank Gerbode, M.D., San Francisco

3:50—Long-term Results of the Surgical Treatment of Congenital Heart Defects—Saul Robinson, M.D., San Francisco

4:10—Questions and Answers Session

Acceptable for Group A Credit under
the CMA Certification Program

*Special Joint Meeting with the CMA Sections
on Internal Medicine and Radiology*

SUNDAY, FEBRUARY 13

9:30 a.m.—Continental Ballroom #5

(see page 21)

SUNDAY, FEBRUARY 13

Continental Ballroom #4

Physician Responsibility and Drug Abuse

*Presented jointly by the CMA Committee on Dangerous Drugs
and the CMA Committee on Alcoholism*

Treatment and Prevention of Drug Abuse and Addiction in Private Practice

Chairman: William F. Quinn, M.D., Los Angeles

9:00—Introductory Remarks: William F. Quinn, M.D., Los Angeles

9:15—The Management of Barbiturate and Hypnotic Overdoses—David E. Smith, M.D., San Francisco

9:45—Methadone: Its Appropriate Use—speaker to be announced

10:45—Recess

11:00—Do You Encourage or Prevent Drug Abuse?—Edward R. Bloomquist, M.D., Glendale

11:30—Why Do They Drop Out and Turn On?—Stanley Einstein, Ph.D., Newark, New Jersey, by invitation

12:00—Questions and Answers Session

12:30—Lunch Break

Treatment of Alcoholism in the General Hospital

Chairman: Nicholas J. Khoury, M.D., Los Angeles

2:00—Introductory Remarks

2:10—Alcoholism and the Hospital—Jack T. Gordon, M.D., San Francisco

2:30—Implications of the Admission of Alcoholics to the General Hospital—speaker to be announced

2:50—Recess

3:00—Established Treatment Programs—Nicholas J. Khoury, M.D., Los Angeles

3:20—National, State, and Community Resources and Cooperation—Loran Archer, Sacramento, by invitation

3:40—Questions and Answers Session

SUNDAY, FEBRUARY 13 Continental Parlors #1 and #2

California Tumor Tissue Registry PATHOLOGY CONFERENCE

*Sponsored by the American Cancer Society, California Division
and the California Medical Association Committee on Cancer*

Tumors and Tumor-like Conditions of the Kidney and Ureter

Chairman: Nancy Warner, M.D., Los Angeles, by invitation

Moderator: James L. Bennington, M.D., San Francisco

9:00 a.m. to 12:30 p.m.

2:00 p.m. to 5:00 p.m.

The registration fee for this Conference is \$50.00, which includes attendance, a set of 25 slides, protocol and agenda. For attendance only, the fee is \$20.00. There is no charge for residents and interns.

Please register with Weldon K. Bullock, M.D., Executive Director or Roger Terry, M.D., Co-Executive Director, California Tumor Tissue Registry, LA County-USC Medical Center, 1200 North State Street, Los Angeles 90033.

Acceptable for Group A Credit under
the CMA Certification Program

VISIT THE EXHIBITS

- Tower Room
- California Room
- North Lounge
- Hilton Plaza
- Franciscan Room

MONDAY, FEBRUARY 14

Continental Ballroom #5

Valentine's Day Symposium on VENEREAL DISEASE

presented jointly by

CMA Section on Preventive Medicine and Public Health

CMA Section on Dermatology

CMA Section on Obstetrics and Gynecology

CMA Section on Urology

CMA Committee on School and College Health

The Bay Area Venereal Disease Association

Chairman: Richard H. Svihus, M.D., Santa Cruz

Current Concepts in Venereal Disease in Clinical Practice

9:00—Introductory Remarks: Ellis N. Mitchell, M.D., Greenbrae

9:10—The Venereal Disease Problem and the Practicing Physician—Warren A. Ketterer, M.D., Berkeley

9:40—Gonorrhea: Local and Systemic—David J. Drutz, M.D., San Francisco

10:15—Recess

10:35—Anorectal Venereal Disease—Gerald M. Feigen, M.D., San Francisco

11:10—Syphilis: the Great Imitator—Denny L. Tuffanelli, M.D., San Francisco

11:45—Business Meeting: PM and PH Section

12:00—Lunch Break

1:30—

Forum on Prevention and Control of Venereal Disease

Moderator: Horace F. Sharrocks, M.D., Sebastopol

Participants:

Aaron J. Fink, M.D., Mountain View (Urologist)

Cleve B. Baker, M.D., Woodland (Dermatologist)

Yoel I. Haller, M.D., San Francisco (Gynecologist)

Ronald M. Wood, Ph.D., Berkeley, by invitation (Microbiologist)

Mabel S. Rickett, M.P.H., Berkeley, by invitation (Health Education Specialist)

Tom W. Robinson, M.D., Newport Beach (School and College Health)

2:45—Questions and Answers Session

Special Showing of a New Film on Venereal Disease
Discussant: Richard Svihus, M.D., Santa Cruz

4:00—Community Prevention and Control of Venereal Diseases—Walter H. Smartt, M.D., Los Angeles, by invitation

MONDAY, FEBRUARY 14 Continental Parlor #3

CMA Committee on Occupational Health

Pollution Problems Have Many Facets

- 9:00—Neurological Sequelae of Acute Poisoning with Organophosphates—Thomas H. Milby, M.D., Berkeley
- 9:30—Impact of New Regulation of Occupational Safety and Health Act on Medical Practice—Marcus M. Key, M.D., Rockville, Maryland, by invitation
- 10:00—Mercurialism: A Mercurial Diagnosis—Irving R. Tabershaw, M.D., Berkeley
- 10:30—Lead Poisoning and the Environment—Charles C. Hine, M.D., Piedmont
- 11:00—How to Rate Disability from Hearing Noise—C. Richard Wolf, M.D., Berkeley, by invitation
- 11:30—Microwaves—Charles G. Merkel, M.D., San Francisco
- 12:00—Questions and Answers Session

MONDAY, FEBRUARY 14 Continental Ballroom #6

CMA Committee on Allied Health Personnel

The Health Care Assistant in California, or the Portent of Assembly Bill #2109 (California's Physician's Assistant Law)

Chairman: Howard B. Kirtland, M.D., San Diego

Moderator: Daniel W. Clark, M.D., San Jose

- 9:00—The Current Position of the Board of Medical Examiners—speaker to be announced
- 9:30—Liability Implications of the Use of the Health Care Assistant—speaker to be announced
- 10:00—Proposed California Training Programs
- PANEL DISCUSSION
- Members of the Panel: to be announced
- 11:00—The Economics of Utilization of the Health Care Assistant
- PANEL DISCUSSION
- Members of the Panel: to be announced
- 12:00—Questions and Answers Session

TUESDAY, FEBRUARY 15

Continental Parlors #7, #8 and #9

SPECIAL CONFERENCE

CMA Committee on the Role of Medicine in Society

Medical education today—for what? for Hippocrates? for the birds? for tomorrow's practice?

9:00—The Committee on the Role of Medicine in Society plans a "happening" which will consider medical education today, medical practice in 1980-2000, and what might be the relationship, if any, between the two.

There will be audience participation.

Committee members: Ralph W. Burnett, M.D., Bakersfield; John B. Dillon, M.D., Los Angeles; Sanford E. Feldman, M.D., San Francisco; Forest J. Grunigen, M.D., Los Angeles; M. M. Haskell, M.D., Long Beach; R. Hewlett Lee, M.D., Palo Alto; Marvin J. Shapiro, M.D., Encino; Malcolm C. Todd, M.D., Long Beach; Malcolm S. M. Watts, M.D., Chairman

Consulting members: Burt L. Davis, M.D., Palo Alto; John T. Saity, M.D., San Mateo

Student members: Bruce Winters, Loma Linda; Hans Dankers, Stanford; Larry Freeman, Irvine; Steve Textor, Los Angeles; Geoffrey Smith, Davis; William Gillanders, San Francisco; Paul Barrett, Los Angeles; Jim Rausch, San Diego, all by invitation

TUESDAY, FEBRUARY 15

Continental Ballroom #6

EMERGENCY AND DISASTER PREPAREDNESS

SYMPOSIUM

CMA Commission on Community Health Services
CMA Committee on Automotive and Traffic Safety
CMA Committee on Disaster Medical Care
CMA Committee on Emergency Medical Care

Program Coordinator: Herbert H. Zimmermann, Jr., M.D., Burlingame

9:00—Introductory Remarks: Herbert H. Zimmermann, Jr., M.D., Burlingame

9:15—

Medical Communications Systems

PANEL DISCUSSION

Moderator: Arnold C. Niemeyer, M.D., Palos Verdes Estates

HEAR in Southern California—Stephen W. Gamble, Los Angeles, by invitation

A Statewide Radio System for Medical Communications—Donald Irwin, Sacramento, by invitation; William McLarty, Berkeley, by invitation

Questions and Answers Session

10:15—

Hospital Emergency Facilities

PANEL DISCUSSION

Moderator: Richard S. Milligan, M.D., Modesto

In the Urban Community—Stephen P. Murphy, M.D., San Diego

In the Rural Community—Donald Nelson, M.D., Redding

Questions and Answers Session

11:15—

Transportation of the Injured

PANEL DISCUSSION

Moderator: Thomas W. Lyons, M.D., La Mesa

The Air Ambulance—Michael N. Cowan, M.D., San Mateo

Questions and Answers Session

12:00—Lunch Break

2:00—

Airport Medical Planning

PANEL DISCUSSION

Moderator: Emile L. Meine, Jr., M.D., Panorama City

Medical Services at Orly Airport—Doctor Georges P. Bergot, Paris, by invitation

Test Exercise "Air Med" at Oakland International Airport—Wayne P. Chesbro, M.D., Berkeley

Airport Disaster Planning—Harold Gibbons, M.D., Salt Lake City, by invitation

Questions and Answers Session

3:30—

Aviation Safety

PANEL DISCUSSION

Moderator: Thomas N. Elmendorf, M.D., Willows

The Shelter Cove Incident—Marvin B. Hays, M.D., Eureka

The San Francisco International Airport "747" Incident—Donald H. Cheu, M.D., South San Francisco

Questions and Answers Session

4:45—Closing Remarks: Herbert H. Zimmermann, Jr., M.D., Burlingame

Page 19

Section Meetings

101st Annual Session

California Medical Association

Hilton Hotel Mason Street San Francisco

Feb. 12 to 16, 1972

Scientific Sessions

GENERAL MEETINGS

Delivery Systems for High Quality Health Care

FIRST GENERAL MEETING

SATURDAY, FEBRUARY 12 Continental Ballroom #6

Interdisciplinary Approaches for High Quality Health Care

- 2:00—Introduction: David C. G. Monsen, M.D., Los Angeles
2:05—The Kaiser Experience—Cecil C. Cutting, M.D., Oakland
2:20—The American Hospital Association Experience—Stephen Morris, Phoenix, by invitation
2:35—Hospital-based Adult Clinics—Homer C. Pheasant, M.D., Los Angeles
2:50—University-based Programs—Baldwin G. Lamson, M.D., Los Angeles
3:05—Hawaiian Approaches to Health Maintenance Organizations—Fred I. Gilbert, Jr., M.D., Honolulu, by invitation
3:20—Private Practice Point of View—Jean F. Crum, M.D., Downey
3:45—

The Problems of Delivery Systems

PANEL DISCUSSION

SECOND GENERAL MEETING

SUNDAY, FEBRUARY 13 Continental Ballroom #6

Computer Applications Toward Delivery of High Quality Care

Chairman: Richard Opfell, M.D., Santa Ana
Moderator: William T. Blessum, M.D., Irvine, by invitation

- 2:00—Keynote Speaker: Donald Lindberg, M.D., Columbia, Missouri
2:40—Self-administered Patient History Taking and Psychological Tests—Steven R. Yarnell, M.D., Seattle, by invitation

- 3:05—Physiological Data Acquisition, Analysis, and Interpretations, (Including ECG, Spirometry, Cardiac Catheterization, etc.)—Lee D. Cady, Jr., M.D., Los Angeles

3:20—Recess

- 3:35—The Computer and the Care of the Critically Ill Patient—Richard D. Yoder, M.D., La Jolla

- 3:50—Characteristics and Evaluation of Man-Machine Communication Interfaces—Ivan R. Neilsen, Ph.D., Loma Linda, by invitation

- 4:05—The Impact on Patient Care of Laboratory Data Acquisition and Reporting Systems and the "Hospital Information System" Environment—Baldwin G. Lamson, M.D., Los Angeles

4:20—

SUMMARY

Alternatives for Delivering Medical Computing Services; Computing and the HMO—William T. Blessum, M.D., Irvine, by invitation

- 4:30—Questions and Answers Session

THIRD GENERAL MEETING

MONDAY, FEBRUARY 14 Continental Ballroom #6

Consumer Education and Participation for High Quality Health Care

- 2:00—Introduction: Thomas A. Gonda, M.D., Stanford, Conference Director

- 2:15—Opening Remarks
Chairman: Leonard J. Duhl, M.D., Berkeley

2:30—

PANEL DISCUSSION

Members of the Panel: Mrs. Eleanor A. Brand, Seattle, by invitation; Lowell Norling, East Palo Alto, by invitation; Miss Faustina Solis, MSW, La Jolla, by invitation; Keith Winton, Livingston, by invitation
Questions and Answers Session

Section Meetings

ALLERGY

Chairman.....MILTON MILLMAN, M.D., San Diego
Secretary.....HAROLD S. NOVEY, M.D., Whittier
Assistant Secretary.....J. GARLAND STROUP, M.D., Sacramento

SATURDAY, FEBRUARY 12 Continental Parlors #8 and #9

Allergy for the Non-Allergist

Co-sponsored by the California Society of Allergy

Moderator: Harold S. Novey, M.D., Whittier

- 9:00—Introductory Remarks—Milton Millman, M.D., San Diego
9:10—Present Status of Alpha-1 Antitrypsin Deficiency in Pulmonary Diseases—Jack Lieberman, M.D., Duarte
9:30—Indications and Techniques for Arterial Blood Gases, Central Venous Pressure, Diffusion Capacity of the Lungs—Archie F. Wilson, M.D., Ph.D., Irvine, by invitation
9:50—Questions and Answers Session
10:00—Symptomatic Therapy of the Diseases of Allergy (Newer Treatment Modalities)—Elliott Middleton, Jr., M.D. Denver, by invitation
10:50—Recess
11:00—Specific Therapy of the Diseases of Allergy (Is Hyposensitization Passe?)—Roy Patterson, M.D., Chicago, by invitation
11:50—Questions and Answers Session
12:00—Luncheon and Business Meeting with the California Society of Allergy

ROUND TABLE DISCUSSIONS

Staggered timetable so that you may attend introductory portions of all sessions

- 2:15—TABLE I—Which Patients Should Have an Allergy Work-up (indications for referral, tests to be done, results to be expected)—Moderators: Elliott Middleton, Jr., M.D., Denver, by invitation; John E. Newland, M.D., Santa Ana
2:15—TABLE II—Pulmonary Function Tests for Asthma—Moderators: Archie F. Wilson, M.D., Ph.D., Irvine, by invitation; Milton K. McDowell, M.D., Kentfield
2:30—TABLE III—Injection Therapy in the Treatment of Allergy—Moderators: Roy Patterson, M.D., Chicago, by invitation; William D. McKee, M.D., Palo Alto
2:30—TABLE IV—Problems of Children with Allergy—Moderators: Paul A. Steinman, M.D., Greenbrae; Stanley P. Galant, Irvine, by invitation

2:45—TABLE V—Sinusitis, Nasal Polyps, and Nasal Allergy: & Medical and Surgical Indications—Moderators: Leon W. Lipson, M.D., Palo Alto; Julian L. Harwell, M.D., Pasadena

2:45—TABLE VI—Air Pollution and Human Health: Role of Air & Cleaning Devices—Moderators: John R. Goldsmith, M.D., Berkeley; William J. Sayer, M.D., Palo Alto

Acceptable for Group A Credit under
the CMA Certification Program

5:30—

Social Hour and Cocktail Party—Members, Wives, and
Guests of California Society of Allergy

ANESTHESIOLOGY

Chairman.....PAUL E. THOMAS, M.D., San Diego
Secretary.....ERIC WEBB, M.D., Los Angeles
Assistant Secretary.....JOHN C. DAMRON, M.D., Palo Alto

MONDAY, FEBRUARY 14

Continental Parlor #7

Hospital Situations

- 9:00—Prevention of Accidents in the Operating Room—David D. Cohen, M.D., Los Angeles
10:15—Anesthetic Management of the Massive Trauma Patient—Ronald D. Miller, M.D., San Francisco
11:30—Business Meeting
12:00—Lunch Break

In conjunction with the Section on Obstetrics and Gynecology

- 2:00—Therapeutic Abortion in a Small Non-teaching Hospital—Charles A. C. Ballard, M.D., Los Angeles
3:30—Anesthesia for Obstetrics in a Small Hospital Without a Formal, Organized Anesthesia Staff—Arthur S. Petoyan, M.D., Granada Hills; Melvyn L. Henkin, M.D., Encino

DERMATOLOGY

Chairman.....ROBERT I. FREEDMAN, M.D., Downey
Secretary.....WILLIAM M. GOULD, M.D., Palo Alto
Assistant Secretary.....T. RICHARD MIHAN, M.D., Los Angeles

SATURDAY, FEBRUARY 12 2:00 p.m.—Stanford Medical
Center: Corvin Skin Clinic
Room A 153

Pre-Convention Meeting

Dermatologic Diseases of the Foot—Clinical case presentations will begin promptly at 2:00 p.m., to be followed by discussion.

SUNDAY, FEBRUARY 13 Continental Parlor #7

Practical Management of Foot Problems in Dermatology

SYMPOSIUM

Chairman: Robert I. Freedman, M.D. Downey

8:30—Office Procedures for Diagnosis of Shoe Dermatitis—Robert M. Adams, M.D., Palo Alto

9:00—New Techniques for Rapid Diagnosis of Fungal Infections—Paul H. Jacobs, M.D., Palo Alto, by invitation

9:30—Early Recognition and Management of Circulatory Problems of the Foot—Eugene M. Farber, M.D., Palo Alto

10:00—Recess

10:15—Office Surgery of the Foot Including a Consideration of Local Anesthesia—Leonard A. Levy, D.P.M., M.P.H., San Francisco, by invitation

10:45—The Evaluation and Management of Traumatic Hyperkeratotic Lesions of the Foot—Tilden H. Sokoloff, D.P.M., M.S., San Francisco, by invitation

11:15— PANEL DISCUSSION

11:50—Business Meeting

GENERAL AND FAMILY PRACTICE

Chairman.....LESTER C. KROTCHER, M.D., San Francisco
Secretary.....A. J. WYATT, M.D., Anaheim
Assistant Secretary.....PETER J. KISTLER, M.D., San Bruno

SUNDAY, FEBRUARY 13 Continental Parlor #3

Coronary Surgery—Diabetes Mellitus

9:00—Welcome: Lester C. Krotcher, M.D., San Francisco

9:10—Introduction: Benson R. McGann, M.D., Los Altos

9:15—Criteria for Coronary Artery Bypass Surgery, or, How to Stop that Coronary Before it Happens—Melvin P. Judkins, M.D., Loma Linda

10:15—Questions and Answers Session

10:30—Recess

10:45—Diabetes Mellitus: Problems, Therapy, and Controversy—Ralph A. Shaw, M.D., Ph.D., Philadelphia, by invitation

11:45—Questions and Answers Session

12:00—Business Meeting

GENERAL SURGERY

Chairman.....MARSHALL J. ORLOFF, M.D., San Diego
Secretary.....JOHN E. CONNOLLY, M.D., Irvine
Assistant Secretary.....ALBERT D. HALL, M.D., San Francisco

MONDAY, FEBRUARY 14 Continental Parlor #8

Co-sponsored by the Northern and Southern
California Chapters of the American College
of Surgeons

12:00—Luncheon Meeting jointly with the Northern California and Southern California Chapters of the American College of Surgeons

Presiding: Marshall J. Orloff, M.D., San Diego

12:45—Luncheon Address: Diverticulitis — Bentley P. Colcock, M.D., Boston, by invitation

Colonic Surgery

1:15— PANEL DISCUSSION

Surgery of Colitis
Lower Intestinal Bleeding
Vascular Insufficiency
Emergency Operations

Moderator: Albert D. Hall, M.D., San Francisco

Members of the Panel: Bentley P. Colcock, M.D., Boston, by invitation; J. Englebert Dunphy, M.D., San Francisco; Earl F. Wolfman, Jr., M.D., Davis

2:15—Recess and Questions

2:30— PANEL DISCUSSION

Biliary and Pancreatic Surgery

The Silent Stone
Common Duct Strictures
Pathophysiology of Stone Formation
Relapsing Pancreatitis

Moderator: Lawrence W. Way, M.D., San Francisco

Members of the Panel: Bentley P. Colcock, M.D., Boston, by invitation; Douglas Pinto, M.D., San Francisco; Gerald W. Peskin, M.D., San Diego, by invitation

3:30—Recess and Questions

3:45—Surgical Aspects of Thyroid Disease—Bentley P. Colcock, M.D., Boston, by invitation

- 4:10—The Endocrinologist's Approach to Thyroid Disorders—
Lindy F. Kumagai, M.D., Davis, by invitation
- 4:30—Hyperparathyroidism—Leon Goldman, M.D., San Francisco
- 5:00—Business Meeting

Acceptable for Group A Credit under
the CMA Certification Program

INDUSTRIAL MEDICINE AND SURGERY

Chairman.....REYNOLD T. SCHMIDT, M.D., Los Angeles
Secretary.....CHARLES G. MERCKEL, M.D., San Francisco
Assistant Secretary.....EDWARD J. O'NEILL, M.D., Woodland

TUESDAY, FEBRUARY 15 Continental Parlor #3

Aviation Medicine in Commercial Airlines Operation

- 9:00—Introduction: Francis R. Schwartz, M.D., San Francisco
- 9:10—Experiences with Expanded Emergency Medical Services
Planning for Airports—Wayne P. Chesbro, M.D., Berkeley
- 9:30—Disruption of Biological Rhythms in Commercial Aviation
—Charles C. Gullett, M.D., Kansas City, by invitation
- 9:50—Selection and Maintenance of Airline Crew Members—
Ludwig G. Lederer, M.D., Ph.D., New York, by invitation
- 10:10—Coffee
- 10:30—The Patient as a Passenger—George J. Kidera, M.D., Chicago, by invitation
- 10:50—Environmental Pollution Control in Air Transport Operations—Robert C. Collins, San Francisco, by invitation
- 11:10—Questions and Answers Session
- 11:45—Business Meeting

You may be reached through
(415) 776-1390

East Lounge—8:30 a.m. to 5:00 p.m.

Saturday, February 12—Wednesday, February 16

INTERNAL MEDICINE

Chairman WILLIAM H. TODD, M.D., Long Beach
Secretary DANIEL W. BLACK, M.D., Hayward
Assistant Secretary .. AUGUSTUS STIEGELER, M.D., San Francisco

SUNDAY, FEBRUARY 13

Continental Ballroom #5

Presented jointly by
CMA Section on Internal Medicine
CMA Section on Radiology
California Society of Internal Medicine
American College of Chest Physicians,
California Division
California Thoracic Society

Pulmonary Diseases

Moderator: Warren M. Russell, M.D., San Francisco

- 9:30—Howard L. Steinbach, M.D., San Francisco
- 9:50—Richard Greenspan, M.D., San Francisco, by invitation
- 10:10—Robert Fraser, M.D., Montreal, by invitation

10:30—

ROUND TABLE

Cancer Diagnosis and Therapy—Robert Fraser, M.D., Montreal, by invitation; Richard Greenspan, M.D., San Francisco, by invitation; Theodore L. Phillips, M.D., San Francisco; Warren M. Russell, M.D., San Francisco

11:00—

PANEL DISCUSSION

Coronary Artery Disease, Radiological Diagnosis and Surgical Treatment

Moderator: Angelo M. May, M.D., San Francisco

Members of the Panel: William J. Kerth, M.D., San Francisco; Robert B. Kalmansohn, M.D., Los Angeles; Julius H. Grollman, Jr., M.D., Los Angeles, by invitation; James V. Maloney, Jr., M.D., Los Angeles; Melvin P. Judkins, M.D., Loma Linda; Roy Jutzky, M.D., Loma Linda

Acceptable for Group A Credit under
the CMA Certification Program

12:00—

Luncheon Meeting

Guest Speaker: E. G. Marshall, who plays the role of David Craig, M.D., Chief of Staff, on the medical segment of NBC's television series "The Bold Ones."

Physicians, wives, and guests are invited. Tickets must be purchased in advance. Send checks (in the amount of \$6.50) to:

Robert Stone, M.D., President
American College of Chest Physicians,
California Division
2930 Summit Street
Oakland, California 94609

MONDAY, FEBRUARY 14

Presented jointly by the Section on Internal Medicine; The California Society of Internal Medicine; and the Departments of Medicine of the University of California, Davis, School of Medicine; School of Medicine, University of California, San Francisco; and Stanford University School of Medicine.

These are simultaneous and informal round table discussions, in which audience participation is anticipated. The groups will recess at 9:50 a.m. and 10:50 a.m., at which times the discussion leaders will move to a different room and continue with the same topic.

Hepatitis—Robert K. Ockner, M.D., San Francisco, by invitation; William Admirand, M.D., San Francisco, by invitation; Martin Brotman, M.D., San Francisco

9:00—	Whitney Room
10:00—	Shasta Room
11:00—	Tamalpais Room

Office Management of Communicable Diseases—Elliot Goldstein, M.D., Davis, by invitation; Austin Brewin, M.D., San Francisco, by invitation

9:00—	Shasta Room
10:00—	Tamalpais Room
11:00—	Whitney Room

Drug Abuse — Emergencies: The Comatose Patient — Charles E. Becker, M.D., San Francisco, by invitation

9:00—	Tamalpais Room
10:00—	Whitney Room
11:00—	Shasta Room
12:00—	Business Meeting

Acceptable for Group A Credit under
the CMA Certification Program

OBSTETRICS AND GYNECOLOGY

ChairmanJESSE A. RUST, M.D., San Diego
SecretaryALAN J. MARCOLIS, M.D., San Francisco
Assistant Secretary ..WILLIAM F. KROENER, JR., M.D., Whittier

MONDAY, FEBRUARY 14 Continental Parlor #9

Clinical Reports

Co-sponsored by the California Division of the
American College of Obstetricians
and Gynecologists

9:00—**Surgical Treatment of Endometrial Adenocarcinoma: An Evaluation**—David W. Keller, M.D., Palo Alto, by invitation
9:25—**Post-Pill Amenorrhea**—Frederick W. Hanson, M.D., Davis, by invitation
9:50—**Monitoring the Fetus**—John S. McDonald, M.D., Los Angeles, by invitation
10:15—Recess

10:45—**The Place of Jet Washer in Clinical Practice**—Thomas Lebherz, M.D., Los Angeles, by invitation

11:10—**Vaginal Tubal Ligation**—William K. Graves, M.D., San Francisco

11:30—Business Meeting

12:00—Joint luncheon with the California Division of the American College of Obstetricians and Gynecologists

Luncheon Address: **The Quality of Life**—T. N. Evans, M.D., Detroit, by invitation

Join the Section on Anesthesiology

Continental Parlor #7

2:00—**Therapeutic Abortion in a Small Non-teaching Hospital** —Charles A. C. Ballard, M.D., Los Angeles

3:30—**Anesthesia for Obstetrics in a Small Hospital Without a Formal, Organized Anesthesia Staff**—Arthur S. Petoyan, M.D., Granada Hills; Melvyn L. Henkin, M.D., Encino

Acceptable for Group A Credit under
the CMA Certification Program

OPHTHALMOLOGY

ChairmanGEORGE K. KAMBARA, M.D., Los Angeles
SecretaryRUSH M. BLODGET, JR., M.D., Redding
Assistant Secretary ..PHILIP D. SHANEDLING, M.D., Los Angeles

SUNDAY, FEBRUARY 13 Continental Parlors #8 and #9

Management of Reading Problems

Moderator: Rush M. Blodget, Jr., M.D., Redding

9:30—Introduction: George K. Kambara, M.D., Los Angeles

9:40—**Problems Confronting the Ophthalmologist** —Earl L. Stern, M.D., San Francisco

10:10—**The Management of Reading Disabilities in the Educational Process: Current Concepts**—H. Glenn Davis, Sacramento, by invitation

10:30—**The Educational System and Training of Teachers in the Area of Reading Disabilities: Concepts and Methods**—Henry Bamman, Ed., D., Sacramento, by invitation

11:00—Recess

11:10—**Present-day Training of Physicians in the Area of Reading Disabilities**—Bayard W. Allmond, Jr., M.D., by invitation

11:40— PANEL DISCUSSION

Questions and Answers Session

11:55—Business Meeting

12:00—Lunch Break

2:00—Child Psychiatrist's Management of Reading Problems—Gerald G. Jampolsky, M.D., Tiburon

2:30—The Management of the Hyperactive Child with a Reading Problem—Helen Gofman, M.D., San Francisco, by invitation

3:00—The Ophthalmologist's Management of Reading Problems—Arthur H. Keeney, M.D., Philadelphia, by invitation

4:00—**PANEL DISCUSSION**

Moderator: Byron H. Demorest, M.D., Sacramento

Questions and Answers Session

ORTHOPEDICS

Chairman ROBERT D. SHLENS, M.D., Los Angeles

Secretary JOHN V. BANTA, M.D., San Diego

SATURDAY, FEBRUARY 12 Continental Parlor #3

The Place of Surgery in the Treatment of Arthritis

9:00—Total Hip Replacement—Richard B. Welch, M.D., San Francisco

9:30—Arthroplasties of the Knee—Theodore R. Waugh, M.D., Orange

9:40—Osteotomies About the Knee—Lionel Saenz, M.D., San Francisco

10:00—Recess

10:20—Reconstructive Surgery of the Hand and Wrist—Paul R. Lipscomb, M.D., Davis

10:40—Foot Reconstructive Procedures—Robert L. Samilson, M.D., San Francisco

11:00—Shoulder and Elbow Reconstructive Procedures—Joseph Pierce Conaty, M.D., Fullerton

11:20—The Rheumatologist's Viewpoint—Ellis Dresner, M.D., Los Angeles, by invitation

11:40—Questions and Answers Session—Moderator: Robert D. Shlens, M.D., Los Angeles

12:40—Business Meeting

OTOLARYNGOLOGY

Chairman HERBERT DEDO, M.D., San Francisco

Secretary PAUL H. WARD, M.D., Los Angeles

Assistant Secretary RICHARD L. GOODE, M.D., Stanford

SUNDAY, FEBRUARY 13 Walnut Suite

9:00—

*Panel discussion in conjunction with the
Section on Neurology*

The Treatment of Facial Nerve Palsy

Moderator: William F. Boyle, M.D., San Francisco

Members of the Panel: J. Carroll Ranseyer, M.D., Los Angeles; Kedar Adour, M.D., Oakland; Jack L. Pulec, M.D., Los Angeles; Austin J. Sumner, M.D., San Francisco, by invitation

10:30—Recess

11:00—Business Meeting

12:00—Lunch Break

1:30

Teakwood Suite

*Panel discussion in conjunction with the
Section on Plastic Surgery*

Complications of Maxillofacial Injuries

Moderator: Richard L. Goode, M.D., Stanford

Members of the Panel: John Wilde, M.D., D.D.S., Fresno; Raymond R. Kauffman, M.D., D.D.S., San Mateo; William M. McGarvey, M.D., San Francisco; Marvin H. Quickert, M.D., San Jose; Morley Barsky, M.D., San Diego

2:30—Microsurgery: Where is It? Where is It Going?—Harry J. Buncke, Jr., M.D., San Mateo

3:00—Business Meeting

PATHOLOGY

Chairman OSMAN H. HULL, M.D., Monterey

Secretary ROBERT S. COX, JR., M.D., San Jose

Assistant Secretary DAVID KORN, M.D., Stanford

SATURDAY, FEBRUARY 12 Continental Parlor #7

Co-Chairmen:

David Korn, M.D., Stanford; Osman H. Hull, M.D., Monterey

9:00—Recent Immunologic Advances in the Diagnosis and Management of Intravascular Coagulation—Thomas S. Edgington, M.D., La Jolla

9:30—Au Antigen—Allen G. Redeker, M.D., Los Angeles

10:00—Standardization of Immunology Tests in the Laboratory—H. Hugh Fudenberg, M.D., San Francisco, by invitation

10:30—Recess

10:45—Clinical and Morphological Aspects of Lymphoproliferative Disorders—Robert Lukes, M.D., Los Angeles, by invitation

11:15—Immunologic Patterns in Lymphoproliferative Disorders—Stebbins B. Chandor, M.D., Los Angeles

11:45—Approaches to Immunotherapy of Cancer—Irving Weissman, M.D., Stanford, by invitation

12:15—Business Meeting

SUNDAY, FEBRUARY 13 Continental Parlors #1 and #2

California Tumor Tissue Registry PATHOLOGY CONFERENCE

*Sponsored by the American Cancer Society, California Division
and the California Medical Association Committee on Cancer
(See page 15)*

PEDIATRICS

Chairman WILLIAM M. JENKINS, M.D., Oakland
Secretary J. HAROLD BATZLE, M.D., Riverside
Assistant Secretary FREDERICK FRYE, M.D., San Diego

TUESDAY, FEBRUARY 15

Rosewood Suite

*Presented jointly by the CMA Section on Pediatrics
and the American Academy of Pediatrics,
Northern California Chapter*

Moderator: William M. Jenkins, M.D., Oakland

9:30— PANEL DISCUSSION

Birthmarks and Moles: "To Act or Not to Act"

Members of the Panel: Alvin H. Jacobs, M.D., San Francisco;
William J. Morris, M.D., San Francisco; Robert G. Wal-
ton, M.D., Modesto

10:15—Questions and Answers Session

10:30—Coffee Break

10:45—*Spirochete, Gonococcus and the Pediatrician*—Warren
A. Ketterer, M.D., Berkeley

11:15—Questions and Answers Session

11:30—*Pregnancy, Abortion and Contraceptions During the
Teen-Age Years*—Sadja Goldsmith, M.D., San Francisco

12:15—Questions and Answers Session

12:30—Luncheon Teakwood Suite

Guest Speaker: Emerson C. Walden, M.D., President of
the National Medical Association, Baltimore, by invita-
tion

2:00— Rosewood Suite

Moderator: J. Harold Batzle, M.D., Riverside

2:00—*Infectious Hepatitis and Prospects for Vaccines*—Henry
R. Shinefield, M.D., San Francisco

2:30—*Triple Vaccine; Replacement for Single Vaccine?*—Harry
Meyer, M.D., Bethesda, by invitation

3:00—*Smallpox Vaccine: New Vaccines and Old: Pro and Con*
C. Henry Kempe, M.D., Denver, by invitation

3:30—*Your Partner: the State Virology Laboratory*—Edwin H.
Lennette, M.D., Berkeley

4:00—Questions and Answers Session

4:30—Business Meeting

Acceptable for Group A Credit under
the CMA Certification Program

PHYSICAL MEDICINE AND REHABILITATION

Chairman JOSEPH N. VIZZARD, M.D., Los Gatos
Secretary CARRIE E. CHAPMAN, M.D., Los Angeles
Assistant Secretary ... W. HARVEY MOORE, M.D., San Leandro

SATURDAY, FEBRUARY 12

Walnut Suite

Spinal Cord Injury: Medical Support and Long-Term Management Symposium

2:00—Introductory Remarks: Joseph N. Vizzard, M.D., Los
Gatos

Moderator: Gregory Bard, M.D., San Francisco

2:10—*Regional Systems for the Treatment of Spinal Cord In-
jury*—John S. Young, M.D., Phoenix, by invitation

2:40—*Extending the Life of the Spinal Cord Injured Patient*—
A. Estin Comarr, M.D., Long Beach

3:15—Recess

3:30—*Late Care and Return to Employment of the Spinal
Cord Injured*—Robert G. Taylor, M.D., Sacramento

4:00—*A Fresh Look at Decubiti*—Donald R. Laub, M.D., Stan-
ford

4:30—Questions and Answers Session

4:50—Business Meeting

PLASTIC SURGERY

Chairman DONALD E. BARKER, M.D., Van Nuys
Secretary RAYMOND R. KAUFFMAN, M.D., San Mateo
Assistant Secretary E. C. BROWN, M.D., San Francisco

SUNDAY, FEBRUARY 13

Teakwood Suite

Plastic Surgery of Interest to all Physicians

9:00—*Basic Techniques in Wound Closure*—Mark Gorney,
M.D., San Francisco

9:30—*Fingertip Injuries*—Ernest N. Kaplan, M.D., Stanford

10:00—*The Burn Wound: Thoughts on Present Concepts of
Therapy*—Edward Falces, M.D., San Francisco

10:30—Recess

10:45—*What Can be Done About Thickened Scars?*—Franklin
L. Ashley, M.D., Los Angeles

11:15—*Crash Analysis*—Donald R. Laub, M.D., Stanford

12:15—Lunch Break

1:30— *Panel discussion in conjunction with the
Section on Otolaryngology*

Complications of Maxillofacial Injuries

Moderator: Richard L. Goode, M.D., Stanford

Members of the Panel: John Wilde, M.D., D.D.S., Fresno; Raymond R. Kauffman, M.D., D.D.S., San Mateo; William M. McGarvey, M.D., San Francisco; Marvin H. Quickert, M.D., San Jose; Morley Barsky, M.D., San Diego

2:30—Microsurgery: Where is It? Where is It Going?—Harry J. Buncke, Jr., M.D., San Mateo

3:00—Business Meeting

PREVENTIVE MEDICINE AND PUBLIC HEALTH

ChairmanSTEPHEN A. CORAY, M.D., Ventura
SecretaryRICHARD SVIHUS, M.D., Santa Cruz
Assistant SecretaryDONALD G. RAMRAS, M.D., San Diego

MONDAY, FEBRUARY 14 Continental Ballroom #5

Valentine's Day Symposium on VENEREAL DISEASE

presented jointly by

CMA Section on Preventive Medicine and Public Health

CMA Section on Dermatology

CMA Section on Obstetrics and Gynecology

CMA Section on Urology

CMA Committee on School and College Health

The Bay Area Venereal Disease Association

Chairman: Richard H. Svihus, M.D., Santa Cruz

Current Concepts in Venereal Disease in Clinical Practice

9:00—Introductory Remarks: Ellis N. Mitchell, M.D., Greenbrae

9:10—The Venereal Disease Problem and the Practicing Physician—Warren A. Ketterer, M.D., Berkeley

9:40—Gonorrhea: Local and Systemic—David J. Drutz, M.D., San Francisco

10:15—Recess

10:35—Anorectal Venereal Disease—Gerald M. Feigen, M.D., San Francisco

11:10—Syphilis: the Great Imitator—Denny L. Tuffanelli, M.D., San Francisco

11:45—Business Meeting: PM and PH Section

12:00—Lunch Break

1:30—

Forum on Prevention and Control of Venereal Disease

Moderator: Horace F. Sharrocks, M.D., Sebastopol

Participants:

Aaron J. Fink, M.D., Mountain View (Urologist)

Cleve B. Baker, M.D., Woodland (Dermatologist)

Yosl I. Haller, M.D., San Francisco (Gynecologist)

Ronald M. Wood, Ph.D., Berkeley, by invitation (Microbiologist)

Mabel S. Rickett, M.P.H., Berkeley, by invitation (Health Education Specialist)

Tom W. Robinson, M.D., Newport Beach (School and College Health)

2:45—Questions and Answers Session

3:15—

Special Showing of a New Film on Venereal Disease

Discussant: Richard Svihus, M.D., Santa Cruz

4:00—Community Prevention and Control of Venereal Diseases—Walter H. Smartt, M.D., Los Angeles, by invitation

**You may be reached through
(415) 776-1390**

East Lounge—8:30 a.m. to 5:00 p.m.

Saturday, February 12—Wednesday, February 16

PSYCHIATRY AND NEUROLOGY

ChairmanS. LAWRENCE POMER, M.D., Los Angeles

SecretaryNORMAN I. GRAFF, M.D., San Mateo

Assistant Secretary ..J. CARROLL RAMSEYER, M.D., Los Angeles

SUNDAY, FEBRUARY 13

Toyon Suite

Clinical Approach to the Disturbed Child, for the Use of the Practicing Physician

9:00—Problems of Clinicians in recognizing the meaning of specific symptoms. Discussion of various guidelines and clinical hints and suggestions—with audience participation

PANEL DISCUSSION

Members of the Panel: Charles O. Walton, M.D., Menlo Park; William H. Ayres, M.D., San Mateo; Richard W. Brunstetter, M.D., San Francisco

12:00—Lunch Break

1:30—

Psychiatric and Neurologic Approach

Myth and Reality Regarding Old Age Problems

Co-Chairmen: J. Carroll Ramseyer, M.D., Los Angeles
Leon Epstein, M.D., San Francisco

PANEL DISCUSSION

Members of the Panel: Edward H. Davis, M.D., Beverly Hills;
Leon Epstein, M.D., San Francisco; Harry Weinstein,
M.D., San Francisco; Mrs. Irene Burnside, R.N., M.S.,
Lafayette, by invitation; Miss Mary Lou Clark, M.S.W.,
San Francisco, by invitation

3:30—Recess

3:45—Questions and Answers Session

4:40—Business Meeting

5:00— Continental Ballroom #5

Special Showing "THE WILD CHILD"

Film Discussant: Norman I. Graff, M.D., San Mateo

RADIOLOGY

Chairman WARREN M. RUSSELL, M.D., San Francisco
Secretary GABRIEL H. WILSON, M.D., Los Angeles
Assistant Secretary ROBERT H. REID, M.D., Los Gatos

SUNDAY, FEBRUARY 13 Continental Ballroom #5

Presented jointly by
CMA Section on Internal Medicine
CMA Section on Radiology
California Society of Internal Medicine
American College of Chest Physicians,
California Division
California Thoracic Society

Pulmonary Diseases

Moderator: Warren M. Russell, M.D., San Francisco

9:30—Howard L. Steinbach, M.D., San Francisco

9:50—Richard Greenspan, M.D., San Francisco, by invitation

10:10—Robert Fraser, M.D., Montreal, by invitation

10:30— ROUND TABLE

Cancer: Diagnosis and Therapy—Robert Fraser, M.D.,
Montreal, by invitation; Richard Greenspan, M.D., San
Francisco, by invitation; Theodore L. Phillips, M.D., San
Francisco; Warren M. Russell, M.D., San Francisco

11:00— PANEL DISCUSSION

Coronary Artery Disease, Radiological Diagnosis and
Surgical Treatment

Moderator: Angelo M. May, M.D., San Francisco

Members of the Panel: William J. Kerth, M.D., San Francisco;
Robert B. Kalmansohn, M.D., Los Angeles; Julius H.
Grollman, Jr., M.D., Los Angeles, by invitation; James V.
Maloney, Jr., M.D., Los Angeles; Melvin P. Judkins,
M.D., Loma Linda; Roy Jutzy, M.D., Loma Linda

Acceptable for Group A Credit under
the CMA Certification Program

12:00—

Luncheon Meeting

Guest Speaker: E. G. Marshall, who plays the
role of David Craig, M.D., Chief of Staff, on the
medical segment of NBC's television series "The
Bold Ones."

Physicians, wives, and guests are invited.
Tickets must be purchased in advance. Send
checks (in the amount of \$6.50) to:

Robert Stone, M.D., President
American College of Chest Physicians,
California Division
2930 Summit Street
Oakland, California 94609

UROLOGY

Chairman ROBERT A. C. BRIDGE, M.D., San Diego
Secretary STANLEY A. BROSMAN, M.D., Torrance
Assistant Secretary PATRICK H. MCLIN, M.D., San Rafael

TUESDAY, FEBRUARY 15 Walnut Suite

9:00—Chairman: Robert A. C. Bridge, M.D., San Diego
Business Meeting

9:20—Management of the Injured Ureter—William R. Smart,
M.D., San Rafael

9:50—Clinical Experience with 500 Cases of Kidney Cancer—
Donald G. Skinner, M.D., Los Angeles, by invitation

10:10—Recess

10:25—A Rational Approach to Management of the Neurogenic
Bladder—Emil A. Tanagho, M.D., San Francisco

11:05—Questions and Answers Session
Moderator: Patrick H. McLin, M.D., San Rafael

11:30—Lunch Break

1:30—Practical Evaluation and Management of Urinary Cal-
culi—Hibbard E. Williams, M.D., San Francisco, by in-
vitation

2:15—Questions and Answers Session

2:30—The Role of Intestinal Enterobacteria in Women's Recur-
rent Urinary Infections—Thomas A. Stamey, M.D., Stan-
ford

3:00—Recess

3:15—Washout and Backflow in Urinary Infection—Frank Hin-
man, Jr., M.D., San Francisco

3:45—Questions and Answers Session

Moderator: Patrick H. McLin, M.D., San Rafael

WOMAN'S AUXILIARY

FORTY-SECOND ANNUAL CONVENTION

FEBRUARY 12-16, 1972

Headquarters: Hilton Hotel, San Francisco

Convention Chairman: Mrs. Robert Gobar

Convention Co-Chairman: Mrs. Norman C. Fox

REGISTRATION: Bellagio Room

Saturday, February 12—9:00 a.m. to 4:00 p.m.

Sunday, February 13—9:00 a.m. to 4:00 p.m.

Monday, February 14—8:00 a.m. to 4:00 p.m.

Tuesday, February 15—8:00 a.m. to 10:00 a.m.



MRS. JOHN L. GALLAGHER
President

SATURDAY, FEBRUARY 12—Pre-Convention

4:00 p.m.—Presentation of Mrs. John L. Gallagher, Auxiliary President, to CMA House of Delegates, Imperial Ballroom

SUNDAY, FEBRUARY 13

9:00 a.m.—Executive Committee Breakfast Meeting, President's Suite

1:30 p.m.—Pre-Convention Board Meeting, Rosewood Suite

7:00 p.m.—President's Reception, Continental Ballrooms #4 & #5

MONDAY, FEBRUARY 14

8:30 a.m.—Opening Session of House of Delegates, Imperial Ballroom

12:00 noon—Social Hour, Continental Ballroom #4

12:30 p.m.—President's Luncheon, Continental Ballroom #4

3:00 p.m.—Afternoon Session of House of Delegates, Imperial Ballroom

TUESDAY, FEBRUARY 15

8:30 a.m.—Final Session of House of Delegates, Imperial Ballroom

1:30 p.m.—Presentation of Mrs. Ward L. Hart, Incoming Auxiliary President, to the CMA House of Delegates, Imperial Ballroom

3:00 p.m.—Post-Convention Board Meeting, Continental Parlor #3

WEDNESDAY, FEBRUARY 16

8:30 a.m.—Orientation Meeting, Continental Parlor #3

HOSPITALITY CENTER—Bellagio Room

Sunday, February 13—9:00 a.m. to 4:00 p.m.

Monday, February 14—8:00 a.m. to 4:00 p.m.

Tuesday, February 15—8:00 a.m. to 10:00 a.m.

Instant Breakfast (Roll & Coffee) served Sunday through Tuesday—Bellagio Room—50 cents

Information Booth—Bellagio Room



MRS. WARD L. HART
President-Elect

House of Delegates • 1972 Annual Session

AGENDA

Imperial Ballroom, Hilton Hotel

Speaker William F. Quinn, Los Angeles
Vice-Speaker Joseph F. Boyle, Los Angeles
Secretary Helen B. Weyrauch, San Francisco

FIRST MEETING, Saturday, February 12, 1972

REGISTRATION—3:00 p.m.

MEETING STARTS—4:00 p.m. SHARP

1. Call to order.
2. Announcement of Reference Committees and Miscellaneous Announcements.
 - (a) Committee on Credentials. (Delegates must register with the Committee.)
 - (b) Reference Committee on Community and Environmental Health. (Reference Committee A.)
 - (c) Reference Committee on Government Medical Programs. (Reference Committee B.)
 - (d) Reference Committee on Medical Economics, Insurance and Prepayment. (Reference Committee C.)
 - (e) Reference Committee on Scientific and Educational Activities. (Reference Committee D.)
 - (f) Reference Committee on Public and Professional Relations. (Reference Committee E.)
 - (g) Reference Committee on Finance. (Reference Committee F.)
 - (h) Reference Committee on Constitution and By-laws. (Reference Committee G.)
 - (i) Reference Committee on California Blue Shield. (Reference Committee H.)
3. Honored Guests.
 - (a) Fifty-year members.
 - (b) Past Presidents.
 - (c) Allied Health Groups.
 - (d) SAMA Students.
4. Report of Committee on Credentials, and Organization of the House of Delegates—Roll Call.
5. Recognition of President of the Woman's Auxiliary to the CMA—Mrs. John L. Gallagher.
6. Address by President—Roberta F. Fenlon.
7. Report of the President—Roberta F. Fenlon.
8. Report of the President-Elect—Jean F. Crum.
9. Report of the Speaker and Vice-Speaker of the House of Delegates—William F. Quinn and Joseph F. Boyle.
10. Report of the Trustees of the California Medical Association—Roberta F. Fenlon.
11. Report of Physicians' Benevolence Fund, Inc.—Roberta F. Fenlon.
12. Report of the Secretary—Helen B. Weyrauch.
13. Report of the Editor—Malcolm S. M. Watts.
14. Report of the Executive Director—Robert L. Thomas.
15. Report of Legal Counsel—Hassard, Bonnington, Rogers & Huber.
16. Report of the Executive Committee—Roberta F. Fenlon.
17. Report of the Council—John T. Saidy, Chairman.
18. Report of California Blue Shield Trustees—Carl E. Anderson, Chairman of the Board of Trustees.
19. Reports of Commissions.
 - (a) Commission on Medical Services—Robert M. Bartel, San Diego.
 - (b) Commission on Public Agencies—Joseph P. O'Connor, Pasadena.
 - (c) Commission on Community Health Services—James H. Yant, Sacramento.
 - (d) Commission on Communications—James C. MacLaggan, San Diego.
 - (e) Commission on Member Services (was Professional Welfare)—Harrison E. Silver, Riverside.
 - (f) Judicial Commission—W. Philip Corr, Riverside.
 - (g) Commission on Health Manpower (was Allied Health Professions and Services)—Dan W. Clark, San Jose.
 - (h) Commission on Health Facilities (was Hospital Affairs)—Joseph W. Telford, San Diego.
 - (i) Commission on Legislation—Frederick Ackerman, Pleasant Hill.
 - (j) Commission on Peer Review—Robert M. Bartel, San Diego.
 - (k) Scientific Board—C. John Tupper, Davis.
20. Reports of Other Committees.
 - (a) Bureau of Research and Planning—Henry V. Eastman, Tustin.
 - (b) Role of Medicine in Society—Malcolm S. M. Watts, San Francisco.
 - (c) Organizational Review and Planning—E. Kash Rose, Napa.
 - (d) Finance Committee—Henry V. Eastman, Tustin.
 - (e) Medical Executives Conference—Edgar H. Colvin, Monterey.
 - (f) Delegates to the AMA—Samuel R. Sherman, San Francisco.
21. Old and unfinished business.
22. New Business.
23. Adjournment.

CALPAC REPORTS

Immediately Following the Opening Session
of the CMA House of Delegates

SECOND MEETING, Tuesday, February 15, 1972, at 1:30 p.m.

(To be recessed and reconvened at 9:00 a.m. Wednesday, February 16.)

ORDER OF BUSINESS

1. Call to order.
2. Supplemental report of Credentials Committee—Roll Call.
3. Introduction of President-Elect of Woman's Auxiliary—Mrs. Ward L. Hart.
4. Address by President-Elect—Jean F. Crum.
5. Secretary's announcement of Council's selection of time and place for the 1973 Annual Session.
6. Election of Officers:
 - (a) President-Elect.
 - (b) Speaker.
 - (c) Vice-Speaker.
 - (d) Councilors (three-year terms):
 - (1) First District—Office #2—New Office to begin in 1972.
First District—Imperial and San Diego Counties.
 - (2) Fourth District—Office #5—Joseph P. O'Connor, Pasadena, (term expiring).
 - (3) Fourth District—Office #8—Harold E. Wilkins, Downey, (term expiring—filled unexpired term of Jean F. Crum).
Fourth District—Los Angeles.
 - (4) Sixth District—Office #1—Arthur F. Howard, Fresno.
 - (5) Sixth District—Office #2—New Office to begin in 1972.
Sixth District — Amador, Calaveras, Fresno, Kern, Kings, Madera, Mariposa, Merced, San Joaquin, Stanislaus, Tulare and Tuolumne Counties.
 - (6) Eighth District—Office #1—Albert G. Clark, San Francisco.
Eighth District—San Francisco.
 - (7) Ninth District—Office #1—Harold Kay, Oakland.
Ninth District—Alameda and Contra Costa Counties.
 - (e) Delegates to the American Medical Association (Delegates and Alternates to the American Medical Association are elected for terms of two calendar years. The Delegates and Alternates to be elected at this meeting will serve for two calendar years starting January 1, 1973,* except as otherwise noted).
 - (1) John G. Morrison, San Leandro (term expiring).
 - (2) William F. Quinn, Los Angeles (term expiring).
 - (3) Robert C. Combs, Irvine (term expiring).
 - (4) Homer C. Pheasant, Los Angeles (term expiring).
 - (5) Alfred J. Murrieta, Los Angeles (term expiring).
 - (6) Leon P. Fox, San Jose (term expiring).
 - (7) *Arlo A. Morrison, Ventura:
 - (a) *Retiring—fill unexpired 1972 term.
 - (b) (regular term expiring).
 - (8) Robb Smith, Orange Cove (term expiring).
 - (9) Herman H. Stone, Riverside (term expiring).
 - (10) Malcolm C. Todd, Long Beach (term expiring).
 - (11) Jack E. Vaughan, Bakersfield (term expiring).
 - (12) Carl E. Anderson, Santa Rosa (term expiring).
 - (13) Joseph F. Boyle, Los Angeles (term expiring).
 - (f) Alternates to the American Medical Association: (terms of all incumbents expiring. All offices for two year terms starting January 1, 1973, except as otherwise noted).
 - (1) Frederick Ackerman, Pleasant Hill (alternate to John G. Morrison).
 - (2) H. Russell Fisher, Glendale (alternate to William F. Quinn).
 - (3) Frank A. Rogers, Whittier (alternate to Robert C. Combs).
 - (4) Elmer C. Werner, El Centro (alternate to Homer C. Pheasant).
 - (5) H. Dean Hoskins, Oakland (alternate to Alfred J. Murrieta).
 - (6) R. Hewlett Lee, Palo Alto (alternate to Leon P. Fox).
 - (7) John T. Saidy, San Mateo (alternate to Arlo Morrison).
 - (8) James H. Yant, Sacramento (alternate to Robb Smith).
 - (9) Marvin J. Shapiro, Encino (alternate to Herman H. Stone).
 - (10) Donald R. Fitch, Los Angeles (alternate to Malcolm C. Todd).
 - (11) Ralph W. Burnett, Bakersfield (alternate to Jack E. Vaughan).
 - (12) Jean F. Crum, Downey (alternate to Carl E. Anderson).
 - (13) Jokichi Takamine, Los Angeles (alternate to Joseph F. Boyle).
7. Election of California Blue Shield Trustees (three-year terms):

Report of CMA Council as Nominating Committee. Incumbents, terms expiring:

*Carl E. Anderson, Santa Rosa
James W. Goettle, Tulare (presently completing unexpired term of Ralph W. Burnett)
Jean F. Crum, Downey
Carl Goetsch, Berkeley
*M. M. Haskell, Long Beach
Mr. Harold Furst, Regional Vice President (Bank of America-Berkeley)

*Ineligible for re-election
8. Announcement by Secretary.

Council's nominations of members of Commissions and Committees. (For approval by the House of Delegates).
9. Reports of Reference Committees:
 - (a) Report of Reference Committee A on Community and Environmental Health.
 - (b) Report of Reference Committee B on Government Medical Programs.
 - (c) Report of Reference Committee C on Medical Economics, Insurance and Prepayment.
 - (d) Report of Reference Committee D on Scientific and Educational Activities.
 - (e) Report of Reference Committee E on Public and Professional Relations.

- (f) Report of Reference Committee F on Finance.
- (g) Report of Reference Committee G on Constitution and Bylaws.
- (h) Report of Reference Committee H on California Blue Shield.
- 10. Unfinished Business.
- 11. New Business.
- 12. Presentation of Officers:

- President — Presentation of Plaque to President Roberta F. Fenlon.
- President-Elect.
- Speaker.
- Vice-Speaker.
- 13. Approval of Minutes. (Committee to edit.)
- 14. Adjournment.

WILLIAM F. QUINN, M.D., *Speaker*
HELEN B. WEYRAUCH, *Secretary*

Proposed CMA Constitutional Amendments

FOR ACTION IN 1972

Two Constitutional amendments were introduced in the 1971 House of Delegates. Under the terms of the Constitution these amendments must lie on the table until the next regular meeting of the House of Delegates.

These proposed amendments are shown here for the information of the membership. In addition, the proposed Constitutional amendments are required to be printed in two issues of CALIFORNIA MEDICINE before it comes before the House of Delegates for action.

VOLUNTARY MEMBERSHIP IN CMA AND AMA BY A MEMBER OF A COMPONENT COUNTY MEDICAL ASSOCIATION

ARTICLE I, SECTION 3

Constitutional Amendment 1-71 Committee G
Introduced by: Allan K. Briney, M.D.

WHEREAS, the present Bylaws of the CMA make membership in the CMA and AMA compulsory to all members of a component county medical society; and

WHEREAS, we, as a profession, vigorously defend the principle of "freedom of choice" in health care, yet deny individual members of county medical societies the freedom of deciding whether or not they wish to belong to the CMA or AMA; and

WHEREAS, each physician is quite capable of deciding whether there are sufficient advantages or insufficient advantages to maintaining membership in all three organizations; and

WHEREAS, mandatory membership in one organization (CMA and AMA) in order to maintain membership in another (local medical society) significantly interferes with the privilege of setting priorities as to organizational commitments, such as belonging to specialty societies; and

WHEREAS, many individual "grass roots" county medical society members feel the CMA Council and officers, and the AMA Board, officers and delegates do not generally reflect their attitudes and concerns; and

WHEREAS, in many states a local county medical association member may decide for himself whether he also wishes to maintain membership in the state and national medical associations, e.g., New York and Massachusetts; and

WHEREAS, professional liability insurance carriers have no requirements about CMA or AMA membership for coverage of a county medical society member; and

WHEREAS, insurance brokers are delighted to sell insurance of all kinds under a variety of different organizational arrangements, making it no significant advantage to belong to the CMA or AMA for insurance enticements; and

WHEREAS, in a free and democratic society it would seem reasonable and consistent that membership in all medical societies should be voluntary, with each society attracting members on its own merits; and

WHEREAS, when a local county medical association collects dues for a state and national medical association, the individual dues-payer tends to lump all these dues together as "county medical society's dues," feeling he may not be "getting his money's worth"; and

WHEREAS, recent events in higher levels in AMA politics indicate that a group which does not represent the view of the majority of practicing physicians has assumed control over AMA policy, with the result that physicians in private practice (the mainstream of American medicine) are being asked to accept ideas such as compulsory or "universal" national health insurance that the

AMA opposed as recently as 1965, and with the result that an effort to create a Council on Private Practice was voted down by steamroller tactics in the House of Delegates, and with AMA failure to oppose interference with the practice of medicine by the Department of H.E.W.; and

WHEREAS, there is widespread feeling among local county medical association members that the CMA and AMA have long ago lost their "grass roots" contact and cannot speak authoritatively for the medical profession; now, therefore, be it

Resolved: That Article I, Section 3, be amended as follows:

This Association is an organization composed of the component societies and their members who are members of this Association, the House of Delegates, the Council, the Scientific Board, the Scientific Assembly, Bureaus, Commissions and Standing Committees.

ACTION: Tabled for one year. To be acted upon at the 1972 meeting of the House of Delegates.

(TERMS OF OFFICE—COUNCILORS)
ARTICLE III, PART B, SECTION 12

Constitutional Amendment 2-71

Committee C

Introduced by: David B. Horner, M.D.

WHEREAS, the Councilors of the California Medical Association are elected to serve a term of three years; and

WHEREAS, there is no restriction on the number of terms that a Councilor can be elected and serve; now, therefore, be it

Resolved: That Article III, Part B, Section 12, of the Constitution of the California Medical Association be amended as follows: "Section 12.—Councilors: Terms of Office. Councilors shall serve for a term of three (3) years; one-third to be elected in each year. A Councilor shall not serve more than three (3) consecutive terms of office."

ACTION: Tabled for one year. To be acted upon at the 1972 meeting of the House of Delegates.

Reports of officers, commissions and committees of the California Medical Association, together with the following audited financial statements for the fiscal year ended June 30, 1971, are printed in the Annual Report Bulletin, which is distributed to Delegates and Alternates before the meeting of

the House of Delegates. The Bulletin is also available to any member of the Association on request directed to Robert L. Thomas, Executive Director, California Medical Association, 693 Sutter Street, San Francisco, California 94102.

FINANCIAL REPORTS

CALIFORNIA MEDICAL ASSOCIATION AND TRUSTEES OF THE CALIFORNIA MEDICAL ASSOCIATION

(See pages 32 to 36)

REPORT OF

Certified Public Accountants

CALIFORNIA MEDICAL ASSOCIATION:

We have examined the balance sheets of California Medical Association and Trustees of California Medical Association at June 30, 1971, and the related statements of income and expenses for the year then ended. Our examinations were made in accordance with generally accepted auditing standards, and accordingly included such tests of the accounting records and such other auditing procedures as we considered necessary in the circumstances.

In our opinion, the statements referred to above present fairly the financial positions of California Medical Association and Trustees of California Medical Association at June 30, 1971, and the results of their operations for the year then ended, in conformity with generally accepted accounting principles applied on a basis consistent with that of the preceding year.

JOHN F. FORBES & COMPANY

San Francisco, California
August 6, 1971

**CALIFORNIA
MEDICAL
ASSOCIATION**

(A Nonprofit Association)

Balance Sheet,
June 30, 1971
and 1970, and
Comparison

	JUNE 30		Increase (Decrease)
	1971	1970	
ASSETS			
CASH	\$ 118,028	\$ 62,426	\$ 55,602
UNITED STATES TREASURY BILLS, AT COST		1,074,032	(1,074,032)
CERTIFICATES OF DEPOSIT—VARIOUS MATURITIES TO JANUARY 14, 1972	1,250,000		1,250,000
ACCOUNTS RECEIVABLE, NET	116,993	115,476	1,517
ACCRUED INTEREST	8,586	11,586	(3,000)
NOTES RECEIVABLE:			
Central California Blood Bank	56,287	71,000	(14,713)
Other	1,600	2,400	(800)
Total notes receivable	57,887	73,400	(15,513)
PREPAID EXPENSES AND OTHER ASSETS:			
Retirement program premium (Note 1)	24,434	19,142	5,292
Insurance	5,102	4,114	988
Deposits	4,346	4,161	185
Other	8,599	7,459	1,140
Total prepaid expenses and other assets	42,481	34,876	7,605
OFFICE FURNITURE AND EQUIPMENT (Note 2)	37,807	44,280	(6,473)
NOTE AND ACCOUNTS RECEIVABLE, AFFILIATED ORGANIZATIONS:			
Trustees of the California Medical Association:			
Demand note with interest at 4% per year	125,000	125,000	
Account receivable	16,138		16,138
	141,138	125,000	16,138
Accounts receivable:			
Six Ninety Three Sutter Publications, Inc.	23,730	5,498	18,232
California Medical Education and Research Foundation, Inc.	1,157	7,665	(6,508)
Other	2,187	4,424	(2,237)
Total note and accounts receivable, affiliated organizations	168,212	142,587	25,625
	<u>\$1,799,994</u>	<u>\$1,558,663</u>	<u>\$ 241,331</u>
LIABILITIES			
ACCOUNTS PAYABLE:			
American Medical Association	\$ 49,270	\$ 80,430	\$ (31,160)
Other	39,421	38,028	1,393
Total accounts payable	88,691	118,458	(29,767)
DUE TO AFFILIATED ORGANIZATION— PHYSICIANS' BENEVOLENCE FUND, INC.	23,775	22,565	1,210
INTERAGENCY COUNCIL ON DRUG ABUSE		2,378	(2,378)
DEFERRED INCOME:			
Dues and subscriptions applicable to the succeeding fiscal year	1,264,588	995,691	268,897
Other		3,480	(3,480)
Total deferred income	1,264,588	999,171	265,417
Total liabilities	1,377,054	1,142,572	234,482
EXCESS OF ASSETS OVER LIABILITIES			
(Schedule 1; Note 3)	422,940	416,091	6,849
	<u>\$1,799,994</u>	<u>\$1,558,663</u>	<u>\$ 241,331</u>

See notes to financial statements.

**CALIFORNIA
MEDICAL
ASSOCIATION**

	JUNE 30		Increase (Decrease)
	1971	1970	
UNRESTRICTED:			
Balance, beginning of year	\$ 254,450	\$ 276,747	\$ (22,297)
Excess of income over expenses for the year	6,849	5,406	1,443
Transfer to restricted	3,424	2,703	721
	3,425	2,703	722
Total	257,875	279,450	(21,575)
Contribution toward Bond Proposition One, not budgeted		25,000	(25,000)
Balance, end of year	257,875	254,450	3,425
RESTRICTED AS TO USE (Note 3) :			
Balance, beginning of year	161,641	158,938	2,703
Transfer from excess of income over expenses	3,424	2,703	721
Balance, end of year	165,065	161,641	3,424
EXCESS OF ASSETS OVER LIABILITIES	\$ 422,940	\$ 416,091	\$ 6,849

See notes to financial statements.

**Excess of Assets
Over Liabilities
June 30, 1971
and 1970,
and Comparison**

INCOME:			
Membership dues, less portion allocated to subscriptions to CALIFORNIA MEDICINE	\$2,169,690	\$1,905,562	\$ 264,128
Booth rentals at annual session	42,535	42,051	484
Fees, postgraduate courses	15,090	17,362	(2,272)
Fee for collection of American Medical Association dues	25,834	15,269	10,565
Interest earned	54,370	54,926	(556)
Other	64	891	(827)
Total income	2,307,583	2,036,061	271,522
EXPENSES:			
Physicians' Services and Programs	338,035	324,808	13,227
Divisional Programs	1,518,402	1,280,078	238,324
General expenses	374,013	318,027	55,986
	2,230,450	1,922,913	307,537
Contributions	49,208	50,565	(1,357)
Excess of expenses over income—CALIFORNIA MEDICINE	21,076	57,177	(36,101)
Total	2,300,734	2,030,655	270,079
EXCESS OF INCOME OVER EXPENSES	\$ 6,849	\$ 5,406	\$ 1,443

See notes to financial statements.

**Statement of Income
and Expenses
Years Ended
June 30, 1971
and 1970,
and Comparison**

**TRUSTEES OF THE
CALIFORNIA
MEDICAL
ASSOCIATION**
(A Nonprofit Corporation)

**Balance Sheet,
June 30, 1971
and 1970, and
Comparison**

	JUNE 30		Increase (Decrease)
	1971	1970	
ASSETS			
CASH	\$ 125,231	\$ 7,020	\$ 118,211
INVESTMENTS IN MARKETABLE SECURITIES, AT COST:			
U. S. Treasury bills		156,269	(156,269)
Certificates of deposit, maturing July and August 1971, 5%	150,000		150,000
U. S. Treasury bonds, 2½%, various maturities to December 15, 1972 (market value, 1971, \$328,247; 1970, \$923,002)	345,000	1,036,000	(691,000)
Corporate fixed income securities (market value, \$276,126)	278,843		278,843
Listed common stocks (market value, \$423,137)	442,128		442,128
Total investments in marketable securities	1,215,971	1,192,269	23,702
INVESTMENTS IN WHOLLY-OWNED SUBSIDIARIES, AT COST:			
Pacific Magnetic Equipment Tape Co. (Note 4)	9,000	9,000	
Six Ninety Three Sutter Publications, Inc.	1,000	1,000	
Total investments in wholly-owned subsidiaries	10,000	10,000	
ACCRUED INTEREST AND DIVIDENDS	6,991	2,795	4,196
PROPERTIES, AT COST (Note 5):			
Buildings and improvements	407,303	407,303	
Carpets, installation, and other	20,593	19,521	1,072
	427,896	426,824	1,072
Less accumulated depreciation	143,461	139,500	3,961
	284,435	287,324	2,889
Land	180,217	180,217	
Properties, net	464,652	467,541	(2,889)
EQUIPMENT, AT NOMINAL VALUE	1	1	
CASH SURRENDER VALUE OF LIFE INSURANCE (Note 6)	62,275	56,749	5,526
ACCRUED REAL ESTATE TAXES (contra)	25,000	24,000	1,000
PREPAID INSURANCE AND OTHER EXPENSES	2,345	1,806	539
	<u>\$1,912,466</u>	<u>\$1,762,181</u>	<u>\$ 150,285</u>
LIABILITIES			
ACCOUNTS PAYABLE AND ACCRUED EXPENSES:			
Audio-Digest Foundation	\$ 115,842	\$ 2,930	\$ 112,912
California Medical Association	16,138	632	15,506
Due for securities purchased	18,510		18,510
Interest and accrued expenses	1,658	663	995
Total accounts payable and accrued expenses	152,148	4,225	147,923
ACCRUED REAL ESTATE TAXES PAYABLE (contra)	25,000	24,000	1,000
NOTES PAYABLE:			
California Medical Association, payable on demand, with interest at 4% per year—Unsecured	125,000	125,000	
The Connecticut Mutual Life Insurance Company, with deed of trust as collateral (payable in quarterly installments of \$2,506, includ- ing interest at 4¼% per year, to March 1, 1973) (Note 5)	14,029	23,211	(9,182)
Total notes payable	139,029	148,211	(9,182)
TRUST FUNDS (Note 6)	172,510	161,789	10,721
DEFERRED INCOME	515	785	(270)
EXCESS OF ASSETS OVER LIABILITIES (Note 3):			
Balance, beginning of year	1,423,171	1,402,219	20,952
Excess of income over expenses for the year	93	20,952	(20,859)
Balance, end of year	<u>1,423,264</u>	<u>1,423,171</u>	<u>93</u>
	<u>\$1,912,466</u>	<u>\$1,762,181</u>	<u>\$ 150,285</u>

See notes to financial statements.

	YEAR ENDED JUNE 30		Increase (Decrease)
	1971	1970	
INCOME:			
Net income (loss) from rental properties	\$ 17,848	\$ (3,135)	\$ 20,983
Interest	35,781	33,831	1,950
Dividends:			
Listed common stocks	1,108		1,108
Pacific Magnetic Equipment Tape Co.	1,800	3,600	(1,800)
Gain (loss) on sale of investments	(29,264)	941	(30,205)
	<u>27,273</u>	<u>35,237</u>	<u>(7,964)</u>
EXPENSES (other than property)—			
Professional fees, insurance, and management	18,037	4,793	13,244
	<u>9,236</u>	<u>30,444</u>	<u>(21,208)</u>
OTHER CHARGES—PROVISION FOR RETIREMENT OR OTHER BENEFITS OF EMPLOYEES OF AN AFFILIATED ORGANIZATION			
	<u>9,143</u>	<u>9,492</u>	<u>(349)</u>
EXCESS OF INCOME OVER EXPENSES	\$ 93	\$ 20,952	\$ (20,859)

See notes to financial statements.

NOTE:

1. RETIREMENT PROGRAM

In addition to the Group Pension Program which became effective on January 1, 1961, the California Medical Association has arranged for the funding of a Past Service Pension Plan for certain full-time employees. This resulted in an additional liability of \$62,734 which is being amortized over 20 years from January 1, 1966. The Travelers' Insurance Company has underwritten the plan and will furnish annuity contracts as eligible employees retire. Because the current service benefits and all of the benefits for retired employees have already been purchased under the contract, there is a liability only for the unfunded value of vested benefits. This liability amounted to \$18,078 on January 1, 1971. It is neither recorded on the books of the Association nor included in the accompanying balance sheet.

The pension expense for the year was \$43,350. This expense is determined by the underwriter each year, and may vary, depending on new qualifying employees, and credits arising from qualifying employees leaving the Association.

2. OFFICE FURNITURE AND EQUIPMENT—CALIFORNIA MEDICAL ASSOCIATION

Acquisitions prior to July 1, 1966 are carried at a nominal amount of \$1. At May 13, 1966, a firm of appraisers estimated that the sound value of assets then owned was \$104,415. Assets acquired after July 1, 1966, are summarized as follows:

	Cost	Depreciation or Amortization
Office furniture and equipment:		
Owned July 1, 1970	\$71,627	\$28,039
Purchased during the current year	7,774	
Provision for the current year		12,452
Sales and trade-ins	(1,732)	(629)
	<u>77,669</u>	<u>39,862</u>
Leasehold improvements, Sacramento office:		
Cost	3,357	
Amortization		3,357
Written off	(3,357)	(3,357)
Net book value	<u>\$37,807</u>	

An appraisal made by Marshall and Stevens on October 15, 1970, shows the following valuation for equipment, office machines, and furniture:

	Reproduction Cost	Depreciation Reproduction Cost
San Francisco	\$215,257	\$168,781
Los Angeles	4,710	4,045
	<u>\$219,967</u>	<u>\$172,826</u>

3. COMBINED NET WORTH

The Trustees of the California Medical Association is a wholly-owned subsidiary of the California Medical Association. The Trustees hold in trust a large portion of the assets utilized by the California Medical Association. The combined net worth of the two organizations is summarized as follows:

Entity	JUNE 30		Increase
	1971	1970	
California Medical Association:			
Restricted as to use	\$ 165,065	\$ 161,641	\$3,424
Unrestricted	257,875	254,450	3,425
	<u>422,940</u>	<u>416,091</u>	<u>6,849</u>
Trustees of the California Medical Association	<u>1,423,264</u>	<u>1,423,171</u>	<u>93</u>
	<u>\$1,846,204</u>	<u>\$1,839,262</u>	<u>\$6,942</u>

The combined net worth at June 30, 1971 shown in the summary above does not include the following items:

California Medical Association:	
Excess of the appraised value of furniture and office equipment acquired prior to July 1, 1966 over accumulated depreciation and nominal carrying value, approximately	\$ 51,800
Trustees of the California Medical Association—Excess of net worth over Trustees' investment in their wholly-owned subsidiary, Pacific Magnetic Tape Equipment Co., based on that company's unaudited balance sheet at June 28, 1971	67,182
	<u>\$118,982</u>

**TRUSTEES OF THE
CALIFORNIA
MEDICAL
ASSOCIATION**

**Statement of Income
and Expenses
Years Ended
June 30, 1971
and 1970, and
Comparison**

**CALIFORNIA MEDICAL
ASSOCIATION AND
TRUSTEES OF THE
CALIFORNIA MEDICAL
ASSOCIATION**

**Notes to
Financial Statements**

4. WHOLLY-OWNED SUBSIDIARY OF TRUSTEES

The Trustees of the California Medical Association own all of the outstanding stock of the Pacific Magnetic Tape Equipment Co., which was formed for the purpose of merchandising magnetic tape equipment as an adjunct to the activities of the Audio-Digest Foundation.

5. PROPERTIES

The properties held by the Trustees of the California Medical Association are summarized as follows:

	693 Sutter Street	679 Sutter Street	Total
Buildings and improvements	\$329,414	\$ 77,889	\$407,303
Carpets, installation, and other	19,923	670	20,593
	349,337	78,559	427,896
Less accumulated depreciation	124,952	18,509	143,461
	224,385	60,050	284,435
Land	87,400	92,817	180,217
	<u>\$311,785</u>	<u>\$152,867</u>	<u>\$464,652</u>

The property located at 693 Sutter Street, San Francisco, is subject to a deed of trust to The Connecticut Mutual Life Insurance Company as collateral for a note with a balance of \$14,029 at June 30, 1971.

The management has decided to discontinue recording depreciation on the 693 Sutter Street building, which is used almost entirely by the California Medical Association. Proper maintenance is expected to keep the building in good condition.

Appraisals made by Marshall and Stevens on October 15 and December 4, 1970 show the following valuations for the buildings:

	693 Sutter Street	679 Sutter Street
Reproduction cost	\$696,618	\$277,204
Depreciated reproduction cost	<u>\$487,633</u>	<u>\$184,639</u>

6. TRUST FUNDS

These funds are summarized as follows:

For Mr. and Mrs. Ben H. Read	\$ 69,000
Morris Herzstein Bequest (accumulated earnings remitted to the Trustees of the California Medical Association)	22,114
Life insurance retirement plan for legal counsel	62,275
Deferred compensation	19,121
	<u>\$172,510</u>

The Wells Fargo Bank is the trustee under the Morris Herzstein trust. The corpus is invested in 4,480 units of Wells Fargo Bank Common Stock Fund with a value of \$28,189 at June 30, 1971.

The life insurance retirement plan for legal counsel is offset by the cash surrender value of a life insurance policy.

7. LITIGATION

An antitrust suit against the American and California Medical Associations and others is pending in the Federal District Court in San Francisco. Currently the case is in abeyance pending discussions which involve settlement without any monetary payments. Whether or not settlement is effected, it is the opinion of counsel that California Medical Association will successfully defend itself.





